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THE HEART OF A CHILD

Willis J. Potts, M.D., Chicago

• *The emotions aroused in children by encounters with doctors and nurses, by hospital stays and surgical operations, can leave deep and serious psychic scars.*

Especially during prolonged illness, a child needs more than the minimum of attention. Even under the most hygienic surroundings, the child will develop poorly physically and mentally unless it gets essential tender, loving care. This principle is illustrated by cases of fractures and burns that entail long periods of confinement.

Children 3 or 4 years of age requiring hospitalization or surgery are especially sensitive and should not be neglected during visiting hours. Older children sometimes cooperate remarkably well, especially those who come from stable, closely knit rural families.

Deception is bad. The emotional heart of a child is mysteriously moulded by all those with whom it comes in contact, and a child sunned by love, security, and understanding will be able to withstand the storms of illness and pain.

The physical heart of a child is just a piece of living muscle marvelously adapted to its sole function of pumping blood. It is a rugged mechanism that will tolerate the ravages of infection, the scars resulting from impaired blood supply, and the approaches of surgeons' tools. It is the most efficient self-sustaining pump in the world. In a philosophical sense, the heart of a child is a delicate mechanism, sensitive to the slightest wounds of fear, insecurity, indifference, thoughtlessness, and misunderstanding. Many centuries before its physical function was known, the heart was considered the seat of all emotions and impulses, good and bad. From earliest infancy the heart of a child is subject to a constant stream of mental and physical stimuli, but for the purpose of this discourse it reflects the results of stimuli with which it is bombarded during those short phases of life when the infant or child suddenly meets head-on with doctors, illness, hospitalization, and operation.

Child-Doctor Relationship

Little children are afraid of doctors because of previous unpleasant procedures to which they have been subjected. They employ no system of logic in evaluating the virtues of medical or surgical treatment. Primarily they fear needles and "shots." For children's protection physicians have to do unpleasant things to them, such as giving painful immunizing injections and administering antibiotic drugs. Consequently, when taken to a doctor the child promptly bursts forth with, "Are you going to give me a shot?" A child associates the prick of a needle with a white coat or a nurse's uniform. We might as well admit it—until we have completely won the confidence of children we are ogres to them. Children are in a sense like dogs—they instinctively recognize antagonism and intolerance. It is a truism worthy of repetition that a doctor's successful approach to a child is based on a fundamental love of children and a cultivated tolerance of their eccentricities. However, in defense of the doctor, I believe that the screaming, not too ill, uncooperative child, hovered over by indulgent parents carrying on unintelligible baby talk in a vain effort to comfort their little darling, is a trial of patience to any doctor. A carefully developed deaf ear to unjustified screaming, a zealously masked look covering signs of irritation, and a completely camouflaged desire to stuff one's handkerchief in a wide open mouth pay dividends. A little time and even a smile, if authentic, will soon bring peace and cooperation. Interestingly enough, many of the "badly behaved" children become very amenable when they find out that after all the doctor is their friend and is actually trying to help them.

The child reflects the attitude of its parents. The mother who constantly worries about her child's every tiny variation from normal—what may not even be termed an illness—will soon have a child who magnifies complaints and courts disease. The seed of psychosomatic ailments is planted and will bear much fruit in later life. Mothers in general know that about 90% of children's ailments are self-limited, but anxiety about a possible serious illness often overshadows good judgment. Parents neglect their own infirmities, but when their baby is sick—especially the first one—they fly to the doctor. That is good for the pediatrician but not for

From The Children's Memorial Hospital.
Read before the state meeting of the Illinois Heart Association, LaSalle, Ill., on Nov. 17, 1955.

the child. It too soon learns the power of accentuating complaints and thereby obtaining that delightful status of being the center of the stage.

Actually there are few diseases that will not allow a reasonable time for intelligent observation by parents. Those few diseases that require prompt medical attention have such specific and characteristic signs of variation from normal that an observant mother may promptly recognize the need for immediate help. For most of the simple ailments, not severe enough to keep a child away from his favorite television program, it makes little difference whether a tablet of aspirin is given or a bit of goose grease is rubbed on the sore place.

Impact of Hospitalization

The doctor's primary concern is with the effect upon the emotions of the infant or child whose illness is severe enough to require hospitalization and operation. I have often wondered what sort of a scar, how deep and how serious, is left on the heart of a child who is torn from its parents and suddenly tossed into hospital environment associated in its mind with insecurity and pain. Because people get sick, there must be hospitals. Adults are presumably reasonable creatures who when ill go to hospitals more or less willingly because they know they have to do so to get well. Doctors work in hospitals every day and think them wonderful, but as patients, most of them hate hospitals and their routine. Imagine how a child feels. Children's hospitals are marvelous institutions to parents the day they take home their child who was ill and now is well. That does not change the fact that to a child a hospital experience is often a nightmare. Before the age of reason, a child is unable to comprehend why he should have been subjected to the emotional insecurity of separation from his mother. Even the finest hospital falls far short of what an ideal hospital should be. If nursing service were limitless, and if laws of economics could be repealed, there would be no problem. A mother then would simply bring her child to the hospital and deliver it to a nurse well trained in scientific care of children and in the art of substitute motherhood. Whether the child remained in the institution three days or three months would make little difference. Normal development would not be impeded and emotional turmoil would be avoided. It could be as simple as that.

Of necessity, hospital care for children has become extremely complicated and, consequently, has a tendency to become too impersonal. We order intravenously given fluids, blood transfusions, injections of drugs, nasal tubes, blood cell counts, and a host of other things. All are necessary for recovery of the patient, but how can a little child comprehend this and how can residents, nurses, and technicians get their work done if they had to spend two-thirds of their time explaining to unwilling listeners the object of each move? When dealing with immature and uncomprehending minds, parents and doctors have to do the best they can to minimize the rips and tears in the emotional patterns of the children. Little is known about the memory of a child during its first year of life, but it is known that reactions to fear and insecurity manifest themselves early. An infant up to about one year of age is indifferent to physical surroundings but not by any means indifferent to the people who care for him. Ordinarily, it is believed that the infant aged 6 months or less does not care whether the mother is present. Actually, the infant does not care, so long as a substitute mother gives the same tender loving care. Nurses act as substitute mothers. Because they are women, and in their not too subconscious minds are looking forward to the day when they will be caring for their own children, they easily learn the technique of administering tender loving care to the young infant. Whenever possible all infants are fed by a nurse holding the baby on her lap. Sick or well, the infant loves contact. Observe in unspoiled nature how a mother animal guards, fondles, and cares for its young and you will realize the utter folly of the advice to "leave the child alone." An animal outgrows babyhood rapidly, but the human, helpless for years, requires long and constant security provided by mother. The child needs protection and love given by instinct, uninhibited by theoretical advisors and professional baby raisers.

Understanding the Sick Child

Infants require stimulation—auditory, visual, and tactile. Their development—entirely by the route of their senses—must continue during those periods of time that are spent in a hospital. Of course, an illness of a week or two is going to leave no scar. The child's memory of pain is short, and the ability to harbor resentment has not yet developed. Prolonged illness is another story. It has been shown again and again by psychiatrists that infants do poorly in a foundling home where they get a minimum of attention. Even under the most hygienic surroundings, they develop poorly physically and mentally. The mortality rate is higher in these children than it is in even a rather poor home where they get essential tender loving care. This case came to my attention recently. A 6-week-old normal male infant was brought to the hospital with a broken femur. It was necessary to put both legs up in overhead traction. The infant lay on its back 24 hours each day and was fed in that position. Circumstances were such that he had no visitors. After about three weeks the infant lay in his bed in a constantly listless state, indifferent to food and people. He did not cry or fuss—just lay there with eyes half closed and, one might say, shut off from the world. At this time a volunteer worker was assigned to this infant eight hours a day. She fed the baby while supporting his head and shoulders. During waking hours she played with and fondled him. In another three weeks when ready to go home he had gained weight and was smiling, cooing, and acting as a 3-month-old child should. This infant had not been neglected. He had been fed, bathed, and kept clean, but that is not enough for any child sick or well. They need thoughtful stimulation, and that stimulation of their senses is what gives security and pleasure in living, synonymous with growth and development.

An 8-month-old baby girl so severely burned that recovery seemed impossible was kept alive and recovered because of nursing care. Plasma could not be administered fast enough to replace proteins lost from oozing wounds. Only food could keep up the child's strength. It is not easy to get food into a child who has constant

pain and a temperature of 103 to 104 F (39.4 to 40 C) every day. It was accomplished by patience. As soon as the child could be picked up, she was fed on a nurse's lap night and day. She recovered. She has physical but, I am quite sure, no emotional scars. When the mother took her child home she thought a facetious suggestion that she include in the child's name the initials R. N. had been seriously made.

To mothers I suggest that the child be given the attention he craves, sick or well. A sick baby in the hospital should be visited every day, and at the earliest possible date he should be taken home. There is no place in the world like home for a child. Even the poorest home, where there is accord, is better than the finest hospital. If the child must remain in the hospital long, visit often and crowd in as much attention as possible during those few hours. Whatever spoiling may be done during visiting hours will be counteracted during the rest of the day and night. The child will naturally cry when the parent leaves, but return visits will dispel the fear of being forgotten or deserted.

The sensitive 3-year-old or 4-year-old children requiring hospitalization and operation are the ones for whom I am sorry. While seriously ill they have not enough energy to scream for their parents, but the moment they improve they begin hollering for their "mommy." Many, many times I have seen such little children standing in their high-sided cribs, their faces stained with tears and their pupils dilated with fear, sobbing interminably, "I want my mommy." You can pick them up, offer them toys, and tell them over and over that "mommy" is coming. Their only response is more wailing and "I want my mommy now." A 3-year-old child has no sense of time. "Pretty soon" means absolutely nothing. Anything they want, they want right now. A 3-year-old boy had a rather simple operation normally requiring about a five-day stay in the hospital. He was in a ward—no private room was available. When the parents left after visiting hours he began to scream and continued most of the night and the following day until the parents returned. There was nothing to do but let the child go home. No physical complications could be worse than having this youngster tear his emotional system to pieces.

Children from 5 to 8 years of age are often equally unhappy but can be steered into a more equible frame of mind during the long 21 hours between visiting periods, provided there are enough nurses and helpers to give them their time and personal attention. Insecurity and fear, to a far greater degree than is realized, plague these children who are sick and, against their wishes, are forced into a hospital. The best that can be done in the present state of hospital tradition and medical necessity is to prepare them for the unpleasant incidents that suddenly face them and in love and understanding soften the blow to their immature minds. For older children nothing in the field of medicine is finer nor more essential than an understanding nurse, resident, or intern who, with cultivated sixth sense, makes them feel that they have not entered torture chambers but have been admitted to a place where folks are going to help them get well and where they are interested in their happiness.

Child's Reaction to Illness and Hospitalization

It never ceases to be interesting to watch the reaction of children entering a hospital for operation. It varies all the way from childish bravado to sheer panic. A 7-year-old boy was brought in because of a question of hernia. Examination proved there was no hernia; and as the boy left the examining room he made a gesture of wiping sweat from his brow and exclaimed, "Boy, that was a close one." A younger child clarified his position after I had explained to him that he would have to have an operation. He said, "I hate you, you stinker." Another little boy said in response to what he considered bad news, "You know what? Lions eat people and I hope they eat you." One will not have to worry that such children will have repressions.

Children growing up in an atmosphere of freedom will be well-adjusted extroverts if these liberties are balanced with intelligent restrictions. Some children, unfortunately subjected to no limitations at home, expect the same indulgences when entering a hospital. No attempt is made to alter a child's social pattern during a brief hospital stay, but staff members are forced, for the good of all, to impose some limitations upon children who are patients for many months. It has been interesting to observe that children actually enjoy the intelligent restrictions of an orderly life. Children love established routine. When they learn what they may do and what they may not do they become cooperative, are happier, and are more secure than when they are completely unrestricted.

Hospital personnel must deal with every type of child from the overindulged child of supersolicitous parents who expect every whim to be granted upon demand to the affable child who patiently accepts without objection the routine of the hospital. Children, like some adults, learn rapidly that the gentle voice and the affable smile get them much more service than harsh and sullen demands. An interesting observation has been made at Children's Memorial Hospital on the adjustability of children. Patients to be operated upon for congenital heart disease come from many localities and many states. It has become a sort of game to pick the area from which such a patient comes. The percentage of correct guesses eliminates chance as a factor. Children who come from small towns, especially from farms, can be spotted in a moment. They are easy to care for, accept hospital routine, and do not scream when being examined. Say to one of these children, "May I listen to your heart?" and the child lifts up his gown and calmly accepts half a dozen stethoscopes on his chest. Why is this true—if it is? I believe these children are so because they come from stable, closely knit families. Many come from farms where the family is the center of all activity. These children know from experience and few words of direction what they may or may not do. When their parents tell them they are to go to a hospital and must be good boys or girls they are just that. It is routine for them to accept what comes from day to day. The evening before operation parents are naturally on edge. If they were not concerned they would not be quite normal. Outside the door they ask about the danger of the opera-

tion, and they get what they are entitled to—a frank answer. The truth of the matter is that today with good anesthesia, guarded asepsis, antibiotic drugs, and trained surgeons most operations are safer than a cross country trip in an automobile.

Preparation for Operation

At Children's Memorial Hospital the child is told exactly what is going to happen. Often the youngster will ask, "Are you going to cut me?" A bit of license is taken at that point, and he is told, "We are going to operate upon you and fix that sore place." If the child is 3 to 5 years old he is told that in the morning he will be moved in his bed to a special room where he will see nurses and doctors with funny things called masks on their faces. He will be put on an extra fancy table and be allowed to blow up a balloon. As he blows up the balloon he will get sleepy, and when he wakes up he will be back in his room where mommy and daddy will be waiting for him. It is as simple as that. The older child, 6 to 7 years of age, is likewise told in words that he can understand exactly what will happen. After the questions have been answered, the child is content and goes to sleep. The mother is the one who gets the sleeping pill. One child said after the explanation about anesthesia and operation, "You don't have to tell me all that stuff. I know all about it—I saw it on TV."

I began to explain to an 11-year-old girl, on the day before her operation for a patent ductus arteriosus what was expected to be done on the following day. The mother jumped up, grabbed me by the arm, and steered me out of the room. "Nancy doesn't know what she's here for. I don't want her to know. She thinks she's here for another test." I promptly led the mother back into the room and said to Nancy, "Do you know why you are here?" "Sure," she said, "I'm going to have an operation on my heart." You cannot fool children, and, if you try, be prepared for a terrific backfire. When Nancy is 16 she will be fooling her mother and be an expert at it because of her early first-class tutoring. Children get such distorted ideas of hospitals and operations. A 6-year-old girl was admitted to the hospital for an operation. When I entered her room the child was clinging to her mother and sobbing hysterically. Nothing would comfort her. After long questioning about the usual things that cause pain, she finally blurted out, "I don't want to die." Then the full story came out. A few weeks previously one of the children from her room in school had been taken to a hospital for operation and had died. It is easy to understand how her immature mind, knowing nothing about the ailment of her playmate, jumped to the conclusion that all children admitted to a hospital die. She was finally persuaded to go on rounds through the hospital to see other children who had had the same operation she was to have. I shall never forget that little, cold, moist hand in mine as we visited other convalescent patients. One could see the cloud of fear being dispelled as she stared at the children in their beds coloring pictures or playing with toys. She returned to her mother with a smile. Incidentally, she went through the operation and postoperative period without a whimper.

An 11-year old boy who had been in the hospital six months and had had seven operations and more than 20 blood transfusions said to his surgeon when he finally recovered and was about to leave the hospital, "Even after all those operations I still like you." Children are such amazing little creatures. Tell them in simple words why they have to go to the doctor or the hospital or why they have to have an operation and, in most instances, they will cooperate in a fashion that adults might well emulate. Faith and trust are completely unspoiled when children are dealt with honestly. So little effort; so great the reward.

Comment

The mystical heart of a child is a precious and beautiful thing. It is marred only by wounds of a thoughtless and not too intelligent world. In a physical sense the heart is a tough organ; a marvelous mechanism that, mostly without repairs, will give valiant pumping service up to a hundred years. In an emotional sense it is susceptible to wounds of indifference, thoughtlessness, and neglect and during episodes of illness is especially vulnerable. The heart of a child is mysteriously moulded by parents, teachers, playmates, and all those with whom it comes in contact. Physicians wish during those short but violent episodes of illness to avoid wounds that will leave irreparable scars. I am convinced that the heart of a child sunned by love, security, and understanding will be able to withstand the storms of illness and pain.

707 W. Fullerton Ave.

Zinc Oxide.—Zinc oxide is perhaps the most frequently and most voluminously used agent in topical dermatotherapy. Because of an almost total absence of pharmacological discussion in the formal texts on dermatology, its use by the dermatologist is developed in a nebulous, almost subconsciously instinctive manner. The usual concept of its action is probably that of an inert blanket. We could not demonstrate any value as a bacteriostat against several common bacteria. Calamine, used in external preparations for well over 300 years, is a zinc ore found naturally in Europe, England, and America. Exactly how it was introduced into dermatotherapy is not clear, but the fact that some calamines possess reddish or brownish-red colors, approximating skin color, probably was the most important factor in the spread of its use. Because of its wide variation in composition, as well as its inconstancy of color, it was replaced by a synthetic called prepared calamine, made by adding about 0.5% red ferric oxide to white zinc oxide. This is pale pink. Neccalamine, a much more cosmetically acceptable skin cover, made by adding 3% red ferric oxide and 4% yellow ferric oxide to white zinc oxide, enjoyed only a few years of popularity. Principally because of its staining property, it has been deleted from the 10th revision of the National Formulary.

Neo-Zinc Oxide Hyperfine is a new form of chemically pure zinc oxide. By the special technique of its manufacture, its molecular structure has a distortion in its crystal lattice which reflects light so that its color is moderate orange-pink ("flesh," "red," "brick red," "buff red," etc.). The particulate size is extraordinarily small, about 200 A. Aggregates of the particulates can be milled or micronized down to as small as 1 μ. The prepared powder has a characteristic mobility, is easily dispersed when rubbed on the skin, to which it adheres with a dry, palpable tenacity. It combines pharmaceutically as easily in all formulations as does white zinc oxide but is cosmetically as effective a skin cover as the usual cosmetic preparations. Studies of its penetrability and dispersion through the skin by electron microscopy and histologically are in progress. It gives promise of displacing white zinc oxide and calamine in topical dermatotherapy.—Bernard Appel, M.D., L. M. Ohmart, M.Sc., and R. F. Sterner, M.D., Zinc Oxide, *A. M. A. Archives of Dermatology*, April, 1956.

STUDIES ON THE ETIOLOGY AND TREATMENT OF ACUTE RENAL FAILURE

Paul N. Johnstone, M.D., Raymond G. Stone, Ph.D., Harold C. Burdick, Ph.D.
Hobart K. B. Allebach, M.D., Loyy F. Patton, Frank E. Tuller
and
Leo E. Erb, Kansas City, Mo.

• The flow of perfusion fluid through isolated rabbit kidneys was greatly accelerated by the vasodilating action of papaverine. Similar results were obtained when human kidneys were perfused promptly post mortem. In the untreated kidney, intense vasoconstriction so narrowed the blood vessels that the formed elements of the blood could not pass through. This suggested the theory that anuria before death is caused by renal ischemia and should be correctible by the vasodilating action of papaverine.

Eleven patients suffering with acute renal failure were given papaverine. Ten responded promptly with material increases in urinary output. In the average patient, the recommended dosage on the basis of this experience is 0.5 grain (32 mg.) of papaverine hydrochloride injected intramuscularly every 2 hours for 48 hours as an addition to the standard therapy.

The serious nature of acute kidney failure is generally recognized. In civilian practice the mortality from this cause is variously estimated, but it is commonly recognized as high. As this syndrome usually develops as a complication, the primary disease is generally established as the cause of death, and too often the lethal complication is difficult to assess.

The importance of accurate records that disclose a true picture is emphasized by experiences in the United States Army during World War II and in the Korean conflict. Meroney reports, "Early in the Korean war, as in World War II, approximately 90% of the wounded men who developed renal failure died. When a special center for the treatment of renal insufficiency was established in the combat zone of Korea, increased emphasis was placed upon the early recognition and treatment of renal failure in wounded men. Strict attention was focused on urinary output, and patients with a 24-hour urinary volume of less than 500 cc. were transferred promptly to the renal center, where specialized treatment, including artificial kidney dialysis, was available. The mortality rate for patients with renal failure fell promptly to approximately 50%, but there it remained for the duration of the war. This dreadful figure was not reduced further, even though the chemical effects of uremia responded well to methods of treatment then available."[1]

Our group has approached the problem of acute renal failure by commencing our studies at the basic science level, where fundamental information has been obtained. This new information then became the basis for clinical action. We have developed an artificial heart and lung machine with which we have been able to observe the circulation of blood through the isolated kidney. This organ, after the use of anticoagulants and the removal of blood, was excised from the body of anesthetized living rabbits. We confirmed the fact that the kidney immediately undergoes acute failure when it is removed from the body and connected to the artificial heart and lung machine, for the animal's blood could not be pumped satisfactorily through the organ. If the blood cells were removed from the blood, the remaining fluid plasma could be made to circulate satisfactorily. This suggested that the blood vessels of the kidney had narrowed so that formed elements of the blood could not pass through. We also found this condition in the kidney of man.

It seems likely that such ischemia may develop clinically in man. A shock episode may be followed by nonrecovery of the kidney, which remains ischemic. We have been able to show that the addition of papaverine hydrochloride to the blood is followed regularly by vigorous circulation of the blood through a connected kidney. Obviously the addition of this drug dilated narrowed blood vessels. On the basis of these findings, we have treated 11 patients with acute renal failure with this drug.

Operation of Artificial Heart and Lung Machine

In using our artificial heart and lung machine to circulate blood through a rabbit's kidney, the renal artery and vein are separately cannulated, and blood is directed through the vascular system of the kidney (fig. 1). The blood is propelled with compressed air, with constant control of the pressure under which it enters the renal artery. As blood leaves through the renal vein, it is first conducted to a flow meter where volume measurements are automatically made and recorded. From the flow meter the blood is conducted by gravity flow into a tube of glass beads where oxygen (95%) and carbon dioxide (5%) are constantly released. The blood forms a film on the surface of the beads and is oxygenated. After flowing through the tube of glass beads, the blood collects in a funnel beneath. The stem of the funnel is connected to rubber tubing that passes through a Sigma motor pump; thus, the blood is returned to the vessel from which it started. The source of the compressed air is a tank that provides pressure of 20 to 40 lb. A pressure regulator allows a second tank to remain filled to deliver blood into the renal artery under pressure of 100 mm. Hg.

As a kymograph is built into the artificial heart and lung machine, records of the performance of circulation, the perfusion pressure, and time are made simultaneously and continuously throughout each experiment. Plastic

From the University of Kansas City and the Research Hospital.
Statistical analysis of table 1 was made by J. S. Rosen, mathematical physicist, University of Kansas City.

tubes and glass cannulas are utilized throughout in the artificial heart and lung machine, except for a rubber tube that passes through the Sigma motor pump. Facilities for tracer injections of India ink are provided. This apparatus may at first seem complicated, but it is relatively simple to understand and operate. It consists of standard apparatus that has been assembled to accomplish a particular purpose (fig. 1).

Experiments upon the Excised Kidney

The artificial heart and lung machine has enabled us to observe not only the kidneys of lower animals but also the kidney of man. From our studies on the rabbit, we have observed a pattern of performance that we have been able to demonstrate applies also to man.

In experiments on the kidney of rabbits, the animal was anesthetized with ether after receiving heparin sodium injection. The abdomen was opened along the line of the linea alba, and the main portion of the colon and small intestine was lifted out of the abdomen and wrapped in gauze. The inferior vena cava was mobilized from behind the peritoneum. The animal's blood was withdrawn from the vena cava with a large caliber needle attached to a vacuum bottle. This bottle contained 5 ml. of 2.5% anticoagulant sodium citrate solution as well as 2 ml. of heparin sodium. We have regularly obtained about 45-90 ml. of blood.

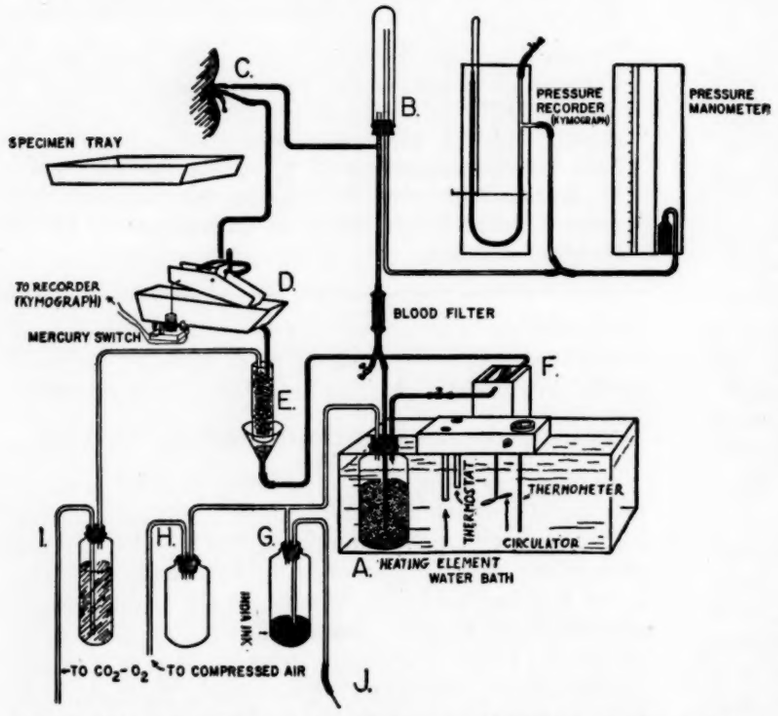

Fig. 1.—The artificial heart and lung machine. *A*, container for blood; *B*, air trap, to protect the pressure recorder and manometer; *C*, point of entry of arterial line to renal artery; *D*, flow meter; *E*, artificial lung; *F*, Sigma motor; *G*, India ink container; *H*, air trap to protect air tank; *I*, bubble indicator, indicating amount of gas passing to glass beads in artificial lung; and *J*, India ink injector.

The left ureter was mobilized and ligated as the first step in excising the left kidney. Ligation of the ureter allowed much longer time for studies; when the ureter was free to drain urine, rapid alteration of the perfusate occurred, especially in kidneys with vigorously circulating blood. The accessory vessels of the kidney poles were also ligated to avoid the rapid loss of the perfusate.

The excised kidney was connected to the artificial heart and lung machine, care being taken to see that air embolism did not occur. This connection was usually effected in from 4 to 20 minutes. Less time was required to reestablish circulation when blood or blood with papaverine hydrochloride was used and more when it was necessary to centrifuge the blood before plasma studies could be made.

The results of these experiments are shown in the table. It has been found that using the difference between the means of analogous perfusate rates of sections A and C of the table as a criterion of judgment, there is by the T test a significant difference in the rates when whole blood or whole blood with papaverine hydrochloride is used. These large differences between the means could have occurred as a result of random errors of sampling much less than once in a thousand times. In other words, the variation in the magnitudes of comparable perfusate rates can safely be attributed to the use of papaverine hydrochloride and not to random errors of sampling.

We have observed the processes of kidneys of man when connected to the artificial heart and lung machine. The machine was set up in the hospital morgue, as it was found necessary for the autopsy to be promptly performed and the kidney removed at once and supplied with blood from the blood bank. In each case the kidney was promptly connected to the artificial heart and lung machine, no effort being made to wash out the vascular system of the kidney. In two instances, this was not accomplished until 150 minutes after death, and the kidneys did not retain the ability to circulate vigorously blood containing papaverine hydrochloride for longer than a few minutes. In two other instances, 125 and 130 minutes after death, the kidneys vigorously circulated blood containing 0.5 grain (0.03 gm.) of papaverine hydrochloride in 200 ml. of blood. In these latter two cases, the blood was perfused at 120 mm. Hg, the first kidney at a maximum rate of 30 ml. per minute and the second kidney at a maximum rate of 70 ml. per minute. Whole blood not containing the drug was then circulated through the first of these kidneys at a maximum rate of only 18 ml. and through the second kidney at a maximum rate of only 16 ml. per minute at 120 mm. Hg.

Although the papaverine hydrochloride was not entirely removed from the kidneys, in these experiments the human kidney circulated blood containing papaverine hydrochloride vigorously but, when whole blood not containing this drug was substituted, the rate of circulation materially decreased. Thus, the human kidney was found to follow the same trend in our experiments as that of the rabbit.

Therapy with Papaverine Hydrochloride

Our first attempts to reverse acute renal failure with papaverine hydrochloride in living man were made in four mortally ill patients who developed reflex anuria; our efforts were directed toward an easier death, there

being no hope of recovery. Patients who are mortally ill and who develop reflex anuria with acute renal failure may pass away in uremic convulsions. Later six other patients not otherwise mortally ill who developed reflex anuria with acute renal failure were also given papaverine hydrochloride as part of their treatment.

Blood Circulation Data of Rabbit Kidney in the Artificial Heart and Lung Machine

Date	Weight of Animal in Lb.	Min. for 20 Cc., Return	Min. to Maximum Return Rate	Total Time of Perfusate	Total Vol. of Perfusate	Cc./Min. at Maximum Rate	Cc./Min. Av. Rate
Section A.—Whole Blood *							
11/21/54	6½	101	77	188	106	1.15	0.52
11/28/54	6	66	66	149	60	1.10	0.40
1/ 9/55	7	203	153	203	15	0.10	0.073
1/16/55	8½	170	133	170	15	0.136	0.088
2/ 6/55	8	132	189	207	40	0.27	0.193
2/13/55	...	84	176	201	75	0.89	0.373
3/24/55	5¾	52.5	60.5	62.9	55	11.70	0.874
4/ 3/55	7½	46	100.8	158.9	490	8.00	3.08
4/14/55	7¼	45.2	84.9	110.7	75	1.24	0.677
4/17/55	6½	104.5	117.8	147.6	55	1.01	0.372
Av.	6.3	100.42	115.8	159.7	98.6	2.56	0.665
Section B.—Blood Plasma * †							
11/18/54	8¾	27.6	54.2	72	50	2.1	0.694
12/ 9/54	9¼	20.3	98	100	175	3.33	1.75
12/29/54	8¼	4.3	1.4	43.3	110	14.28	2.55
1/ 6/55	9½	23.3	15.3	23.3	20	1.36	0.87
1/13/55	9¾	2.0	0.0	72	160	9.4	2.22
1/27/55	9½	5.0	3	63	105	7.04	1.06
2/10/55	8	12.3	10.1	60	80	5.6	1.33
2/17/55	7½	5.2	1.15	30.3	65	18.7	2.16
2/24/55	7¾	12.1	23.8	31	65	2.98	2.16
3/ 3/55	7¾	4	3.4	78.4	210	9.3	2.69
Av.	8.6	11.61	21.04	57.33	104	7.4	1.81
Section C.—Whole Blood with Papaverine Hydrochloride Added *							
12/16/54	6	1.5	5	31.2	300	16.6	9.67
1/ 2/55	7	2.16	6.4	26.5	315	20.0	11.8
1/23/55	8	4.83	16.7	54.4	520	20.0	9.63
1/30/55	7¾	3	4.8	74.6	415	16.5	5.57
2/ 3/55	9½	1.66	1.68	45.7	810	28.5	17.6
2/20/55	6½	2.9	2.6	45.3	388	22.4	8.62
2/27/55	6½	5	6.5	45.25	265	16.0	5.88
3/10/55	...	4	5.3	55.3	120	14.0	2.18
3/17/55	8½	1.87	1.87	41.5	560	28.0	13.48
3/17/55	9¾	2.5	3.08	52.4	720	22.5	13.74
Av.	7.73	2.94	5.39	47.21	441.3	20.45	9.82

* Anticoagulants used: Heparin sodium intravenously and heparin sodium and anticoagulant sodium citrate solution in receiving bottle. Perfusion pressure was maintained at 100 mm. Hg.

† Whole blood was centrifuged to produce plasma, which was separated from cells.

At first large doses of this drug were administered, 4 grains (0.26 gm.) intramuscularly every two hours. Three of the four patients who received large doses developed muscular twitchings and occasional convulsions. Sedation was required. Critical study of their courses soon disclosed that coincidental reversal of renal failure had occurred after only a small amount of the drug had been given. Accordingly the dose was greatly reduced in later patients. Reversal of acute kidney failure was then just as consistent as with the larger doses, and no adverse reactions developed. We presently prefer to treat the average patient having acute kidney failure with 0.5 grain (32 mg.) of papaverine hydrochloride given by intramuscular injection every 2 hours for about 48 hours, as an addition to standard therapeutic approach to this problem. For essential data on these two series of patients, see figure 2. Three patients who were otherwise fatally stricken died. Evidence of nephrosis was not found in any of these patients at autopsy. We regard this observation as significant, for renal ischemia may have been reversed before changes in the nephron could occur.

One patient with acute renal failure developed no increase in urinary output after treatment with papaverine hydrochloride. He developed shock after a second transurethral resection of residual prostatic tissue. He became jaundiced after blood transfusion, and on the second postoperative day inflammation of the right epididymis developed. At autopsy marked infiltration with inflammatory cells was seen throughout both kidneys, and purulent material was found present in many of the tubules.

This patient presented a complicated problem of acute renal failure. No coincidental increase in urine output occurred when administration of papaverine hydrochloride was added to his treatment. Accordingly, we are satisfied that complicated problems of acute kidney failure exist in which acute renal failure will not reverse with papaverine therapy. Chemical poisons, toxins, bacterial infections, new growths, or mechanical changes may produce changes in the kidneys with resulting failure of these organs. Here benefit with papaverine therapy would be possible only if reflex anuria were also a factor.

Summary and Conclusions

In experiments with an artificial heart and lung machine, we found that, when a kidney excised from an animal or from man was connected to the machine, whole blood alone could not be satisfactorily pumped through the blood vessels of the organ. However, we found that, when the blood cells were removed, the remaining fluid plasma could be made to circulate through the blood vessels of the kidney. This suggested to us that the blood vessels of the kidney had narrowed after the excision. We also found that whole blood containing papaverine hydrochloride could be made to circulate

DIAGNOSIS	DID SURGICAL SHOCK PRECEDE ONSET OF ACUTE KIDNEY FAILURE. LOWEST BL. PRESS.	TOTAL FLUID INTAKE ON DAY OF MAXIMUM URINARY SUPPRESSION BEFORE TREATMENT.	TOTAL URINARY OUTPUT DAY OF MAXIMUM SUPPRESSION BEFORE TREATMENT.	TOTAL FLUID INTAKE ON DAY OF MAXIMUM URINARY OUTPUT DURING OR FOLLOWING TREATMENT.	MAXIMUM 24-HR URINARY OUTPUT DURING OR FOLLOWING TREATMENT.	TIME BETWEEN COMMENCING TREATMENT & FIRST DAY OF 500cc. URINARY OUTPUT OR MORE.	MAXIMUM BLOOD LEVEL OF N.P.N.	DURATION OF TREATMENT WITH PAPAVERINE HYDROCHLORIDE.	DEVIATION OF BLOOD LEVEL OF N.P.N. AFTER TREATMENT STARTED.	TOTAL AMOUNT OF PAPAVERINE HYDROCHLORIDE GIVEN.	METHOD OF ADMINISTRATION OF PAPAVERINE HYDROCHLORIDE.
FOUR PATIENTS OTHERWISE FATALLY STRICKEN											
RT. AND LT. FRONTAL CEREBRAL HEMORRH.	YES 80/60	2,600 CC.	150 CC.	1,875 CC.	2,700 CC.	20 HRS.	84	DECREASED TO 52	3 DAYS	92½ GRAINS	INTRAMUSCULAR INJECTIONS
BRONCHOGENIC CARCINOMA (MET.)	NO	NOT DETERMINED	NONE	1,925 CC.	2,025 CC.	12 HRS.	80	DECREASED FROM 68 TO 64 THEN 80	4 DAYS	99 GRAINS	ORAL ADMINISTRATION
CA. STOMACH WITH EXT. LIVER METAST.	YES 96/70	2,450 CC.	380 CC.	1,115 CC.	2,725 CC.	SAME DAY	64	DECREASED TO 55	5 DAYS	90 GRAINS	ORAL ADMINISTRATION
RECENT GASTRECTOMY FOR BLEEDING DUODENAL ULCER—MYOCARDIAL FAILURE.	YES 89/80	4,400 CC.	135 CC.	425 CC.	3,100 CC.	40 HRS. 425 CC.	103	INCREASED TO 103	1 DAY	40 GRAINS	INTRAMUSCULAR INJECTIONS
SIX PATIENTS NOT OTHERWISE FATALLY STRICKEN—ALL PROMPTLY RECOVERED											
CEREBRAL HEMORRHAGE—TRACHEOTOMY	YES 70/40	1,425 CC.	225 CC.	1,350 CC.	1,400 CC.	30 HRS.	64	DECREASED TO 28	1 DAY	4½ GRAINS	INTRAVENOUS INJECTIONS
NON-UNION FRACTURE LT. FEMUR. 35 CM. INTRAMEDULLARY PIN	YES 60/40	2,000 CC.	35 CC.	2,500 CC.	2,125 CC.	26 HRS.	* NOT DETERMINED	NOT DETERMINED	2½ DAYS	12 GRAINS	INTRAMUSCULAR INJECTIONS
LT. FRONTAL PARIETAL GLIOBLASTOMA	YES 66/70	2,500 CC.	240 CC.	1,380 CC.	2,510 CC.	SAME DAY	30	30	3½ DAYS	20 GRAINS	INTRAMUSCULAR INJECTIONS
LARGE VENTRAL HERNIA	YES 68/46	1,550 CC.	250 CC.	1,025 CC.	1,700 CC.	48 HRS.	29	19	7½ DAYS	10 GRAINS	INTRAMUSCULAR INJECTIONS
OLD OSTEOMYELITIS RT. FEMUR-ENTERITIS AFTER SURGERY	YES 9/0	✦ 8,000 CC.	50 CC.	1,670 CC.	4,500 CC.	8 HRS.	64	28	3 DAYS	17 GRAINS	INTRAMUSCULAR INJECTIONS
CYSTOSCOPY AND RETROGRADE STUDIES	BECAME HYPERTENSIVE	2,250 CC.	50 CC.	2,300 CC.	1,700 CC.	24 HRS.	NOT DETERMINED	NOT DETERMINED	1 DAY	1½ GRAINS	INTRAMUSCULAR INJECTION & ORAL ADMINISTRATION

✦ THIS PATIENT DEVELOPED ALBUMINURIA AND HEMATURIA ON THE THIRD DAY OF KIDNEY FAILURE.
✦ LARGE AMOUNT OF FLUID LOSS FROM DIARRHOEA DEVELOPED.

Fig. 2.—Clinical trials of papaverine hydrochloride in two series of patients.

vigorously. We have found no other drug that equals papaverine hydrochloride for this purpose. When blood not containing this drug was substituted in the kidney, a marked slowing of circulation promptly occurred. We found that experimentally produced acute renal failure is due to renal ischemia and that papaverine hydrochloride is a specific drug that reverses it.

Because clinical acute renal failure in man often may occur on this same basis of physiological anatomy, we treated 11 patients who had acute kidney failure with trial doses of papaverine hydrochloride. Ten promptly developed material increases in urinary output coincidental with this therapy. In one patient who did not respond, purulent material was found at autopsy in many of the renal tubules, and marked infiltration with inflammatory cells was seen throughout both kidneys. Here the primary condition was not renal ischemia.

Three of our patients who were mortally ill from other causes developed acute kidney failure. They died within a week after the reversal of their acute renal failure with the administration of papaverine hydrochloride. At autopsy, no evidence of nephrosis was found in any of their kidneys. We regard this as significant, for renal ischemia may have been reversed before changes in the nephron could occur.

Some patients with acute renal failure spontaneously develop satisfactory urinary output. However, if severe ischemia of the kidneys has been present for too long a time, permanent damage to these organs may occur, even though the patient may have seemed to recover. We think it probable that such damage may inaugurate long-term medical problems. As these changes may be so extensive that the patients have not long to live, we try to prevent episodes of shock, for we are satisfied that the frequent association of shock with acute renal failure is more than coincidental. Therapy with papaverine hydrochloride may have a place in preventing severe renal ischemia in such cases.

When we are satisfied that acute renal failure is caused by ischemia, we have concluded that prompt, positive efforts should be made to improve the blood supply of the kidneys with the administration of papaverine hydrochloride. In the average patients 0.5-grain (32 mg.) doses are given by intramuscular injections every 2 hours for about 48 hours as an addition to the standard therapeutic approach.

1110 Bryant Bldg. (6) (Dr. Johnstone).

1. Meroney, W. H.: Uremia-like Symptoms Not Due to Uremia in Battle Casualties, J. A. M. A. **158**: 1513 (Aug. 27) 1955.

REVERSIBLE UREMIC STATES

Franklin H. Epstein, M.D., New Haven, Conn.

• *Renal circulation is sometimes temporarily impaired by cardiac failure; the resultant renal insufficiency is then amenable to treatment of the failing heart. This was seen in a patient in whom digitalization produced a gratifying diuresis, a fall in the nonprotein nitrogen of the blood, and marked symptomatic improvement.*

Renal disease may be either caused or complicated by obstructions lower down in the urinary tract. This is illustrated by a case of anuria with uremia and mild hypertension in which recovery followed the relief of bilateral ureteral strictures.

Hypercalcemia proved to be the cause of albuminuria and uremia in a patient who had been receiving a daily total of 12 gm. of calcium in various forms as treatment for duodenal ulcer. On a diet relatively low in calcium his renal function was restored to normal.

Other treatable causes of renal impairment include dehydration, infection, salt depletion, alkalosis, and loss of potassium. In addition, there are self-limited, reversible types of renal failure. For these reasons the prognosis in uremia is not necessarily hopeless.

There are few clinical problems that tax the patience, the ingenuity, and the judgment of the physician as much as does the treatment of the patient with uremia. The attitude of the doctor who is called upon to treat such a patient is, perhaps understandably, frequently one of hopelessness and resignation. The inexorably downhill course of patients in the terminal stages of chronic glomerulonephritis is well known.[1] As a result, the pale, prostrated, apathetic, or semicomatose patient with uremia is too often helped on his way by a mixture of morphine and "judicious neglect." It is not widely enough appreciated that, even in a patient with advanced nephritis, renal decompensation can be at least partially reversible. Treatment should not be standardized or consist chiefly of masterful inactivity. On the contrary, therapy for the uremic patient should and can be highly individualized, predicated on sound physiological principles, and motivated by a careful and systematic search for those contributory causes of renal decompensation that can be completely or partially reversed by treatment.

In order to appreciate the unique importance of reversible lesions in the treatment of renal insufficiency, it is helpful to understand a few simple mathematical relationships inherent in the way the normal kidney does its job (fig. 1). The chief functions of the kidneys are to remove metabolic waste products and to maintain a constant composition and volume of body fluids. A high level of urea in the blood, although not in itself harmful, is a useful clinical index of the inability of the kidney to perform these functions properly. As an easily measured index, it has an important relationship to the functional reserve of the kidneys. The quantity of urea (Q) formed and excreted is fairly constant from day to day and is related to the amount of protein metabolized. Its excretion is in direct proportion to the amount filtered by the

From Yale University School of Medicine.

Read before the Ninth Clinical Meeting of the American Medical Association, Boston, Dec. 1, 1955.

glomeruli and is therefore proportional to the product of two variables ($Q = kGFR \times P$, where GFR = glomerular filtration rate, P = plasma level of urea = concentration of urea in glomerular filtrate, and k is a proportionality constant). This is the familar equation of the hyperbola. It illustrates the extent of the physiological reserve of the kidneys. Although the concentration of urea in the plasma varies inversely with glomerular filtration rate from the very first reduction in glomerular filtration rate, one-half to three-quarters of both kidneys can be removed before the nonprotein nitrogen level is necessarily elevated above "normal" limits. Fully two-thirds of both kidneys must be removed before concentrating power is impaired.[2] Conversely, if with the patient on a normal diet the level of nonprotein nitrogen is elevated in what appears at first glance to be only unilateral renal disease, the function of the opposite kidney must be assumed to be impaired.

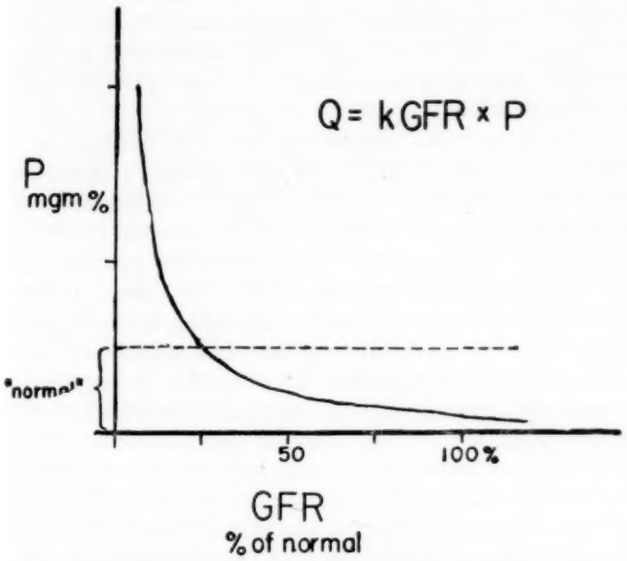

Fig. 1.—Relationships inherent in excretion of urea. Q = quantity of urea formed and excreted; k = a proportionality constant; GFR = glomerular filtration rate; and P = plasma level of urea.

Roughly, we may generalize the relationship between functioning renal tissue and the signs and symptoms of renal failure in the same fashion, as in figure 2. The hyperbolic curve clarifies some aspects of the course of chronic progressive renal disease. For example, one can visualize a slowly progressive process, relentlessly destroying renal substance, which is relatively asymptomatic for many years. When the limits of renal reserve are reached, symptoms appear in swift succession, and the condition of the patient deteriorates rapidly, though there may be little actual acceleration of the rate of pathological destruction of the kidneys.

These curves provide a certain background and philosophy for the treatment of renal disease. The less kidney tissue there is remaining, the more difference a small increment in function makes to the patient. The extent of damage that is reversible is therefore tremendously important. The task of the physician in the treatment of advanced renal disease is to salvage every last bit of renal function—every last nephron. His goal is the discovery and treatment of reversible lesions, no matter how insignificant they may at first appear, because, for a patient on the ascending portion of the curve, a small improvement in function may make the difference between life and death.

Reversible disorders of renal function can be one of two types. In one the disease is self-limited. The damage will eventually resolve and a remission take place, if only the patient does not die in the meantime. The most common causes of acute, reversible, and self-limited renal insufficiency are acute glomerulonephritis and acute tubular necrosis (or lower nephron nephrosis). In the other type of reversible renal dysfunction, the disorder is not self-limited but may progress and even kill the patient if it is not sought out and actively treated. It is to this group of reversible disorders that I should like to confine the following discussion.

Contributory Congestive Heart Failure

One of the most important treatable factors frequently contributing to uremia is congestive heart failure. Heart failure is usually accompanied by a decrease in glomerular filtration rate and renal blood flow, as well as deterioration in other renal functions. In patients with otherwise normal kidneys, congestive failure may produce albuminuria and casts and red blood cells in the urine; but in such cases the urine is usually of high specific gravity and the nonprotein nitrogen level rarely over 50 to 60 mg. per 100 cc. and practically never as high as 90 to 100 mg. per 100 cc.[3] On the other hand in patients with chronic renal disease, a failing heart may make the difference between renal compensation and progressive uremia. With hypoalbuminemia, which is almost always present to some degree in these patients, edema formation can occur with correspondingly less elevation of venous and capillary pressures. Perhaps for this reason, it is sometimes extraordinarily difficult to diagnose heart failure in its early stages without resorting to the use of digitalis as a therapeutic test. Occasionally, a patient may have considerable edema, without apparent dyspnea at rest, orthopnea, pulmonary rales, or measurable elevation of the venous pressure, and still be in heart failure.

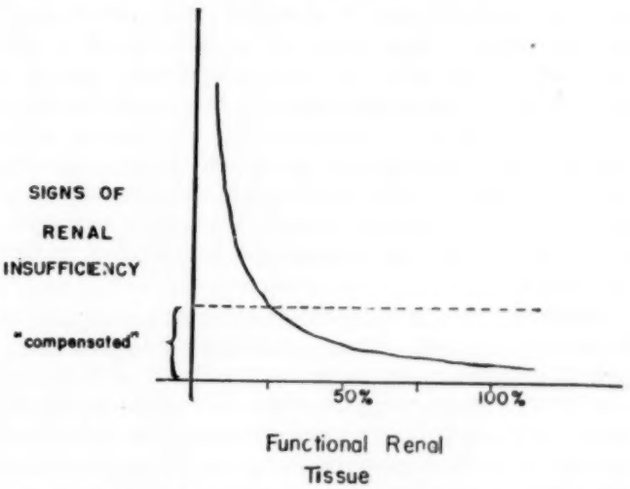

Fig. 2.—Relationship between functioning renal tissue and signs of renal failure.

CASE 1.—A 15-year-old boy with chronic glomerulonephritis had mild hypertension and elevation of venous pressure; the circulation time and heart size were within "normal limits" (table 1). His shins were slightly puffy, but he had a somewhat depressed level of serum albumin to explain this, and he had no signs or symptoms of pulmonary congestion. Despite the paucity of clinical signs of congestive failure, he was digitalized in a therapeutic trial. Immediately there was a gratifying diuresis, and he lost 5 lb. (2.3 kg.). Improved renal function was reflected in a falling level of nonprotein nitrogen and in the disappearance of the patient's symptoms of fatigue and morning nausea.

Infection

It is important to remember that active destruction of renal tissue by pyelonephritis may be going on without fever or shaking chills, leukocytosis, burning or pain on urination, or tenderness in the costovertebral angle. Although these symptoms may occur, especially in an attack of acute pyelonephritis, the only clue to the presence of active renal infection may be the presence of white blood cells and bacteria in a clean or catheterized urine. In every case of chronic renal disease, a urine culture should be made and treatment with the appropriate antibiotic instituted if an infecting organism is found. Again, the resolution of reversible damage may make the difference

TABLE 1.—*Data on Patient with Chronic Glomerulonephritis Before and After Digitalization*

	Before	After
Heart size	Normal	Smaller
Venous pressure, mm. H_2O	130	90
Circulation time, sec.	17	13
Weight, lb.	152	147
Nonprotein nitrogen level, mg. per 100 cc.	100	70
Serum albumin level, mg. per 100 cc.	2.5	2.5
Symptoms	Sluggish and fatigued, morning nausea	Much improved

between compensated kidneys and progressive deterioration. The use of indwelling bladder catheters should be avoided whenever possible in patients with chronic renal disease. Their use invariably leads to infection, often with organisms resistant to antibiotics, and may initiate a necrotizing cystitis. In patients with neurogenic bladders —frequently seen in long-standing diabetes or after poliomyelitis—a stubbornly persistent urinary infection can be controlled only when the bladder is helped to empty completely its residual urine by the use of parasympathetic drugs like neostigmine, bethanechol, or furtrethonium.

Patients with chronic pyelonephritis frequently do not show the widespread vascular damage, the hypertension, and the circulatory deterioration associated with, for example, chronic glomerulonephritis or malignant nephrosclerosis. Partly for this reason, perhaps, at the same level of renal decompensation, the prognosis for these patients is much more hopeful.

Systemic infections—pneumonias and abscesses, as well as infections of the kidney, frequently seem to have a rapidly deleterious effect on renal function in patients with little renal reserve. As a matter of fact, starvation, fever, and injury of almost any type will accelerate the development of azotemia by increasing the breakdown of protein and the load of nitrogenous wastes requiring excretion. Conversely, when these are controlled, the patient may again regain compensation. In an age of antibiotics, in which bacterial endocarditis can be successfully treated, it is important to remember that one of the ways in which this disease can appear is as advanced renal failure, which may improve if the primary disease is cured. The pathological picture in such cases is that of a diffuse glomerular nephritis.

Obstruction

It is important in a case of renal insufficiency first to consider the possibility of lower urinary tract obstruction. The patient with chronic prostatic retention or urethral stricture, with overflow incontinence and infection that can be cleared only by the draining of a pool of stagnant urine, may improve remarkably when his bladder is allowed to empty normally. Chronic partial obstruction results in depression of many renal functions, which is at least partially reversible when the obstruction is relieved.[4] In the bedridden and obtunded patient with chronic renal disease and advanced uremia, unrecognized functional difficulty in bladder emptying, treatable with bethanechol or furtrethonium, may be the cause of rapid and otherwise inexplicable deterioration. A roentgenogram of the abdomen should be part of the initial studies of every patient with uremia and oliguria, since calculi may obstruct both ureters simultaneously or a single ureter when there is only one kidney. Failure to investigate the possibility of ureteral obstruction in such cases may be as disastrous as too vigorous instrumentation of the urinary tract in chronic nephritis or acute tubular necrosis.

CASE 2.—A middle-aged woman was recently admitted to the hospital, having passed no urine for two days. She had mild hypertension and a nonprotein nitrogen level of 180 mg. per 100 cc. Because she had no history of renal disease and had drunk an unknown quantity of questionable alcoholic liquor some days before, she was thought to be suffering from acute tubular necrosis, or lower nephron nephrosis, caused by the ingestion of some poison. This opinion was reinforced when, during the days after admission, she began to void progressively larger quantities of dilute urine with fixed specific gravity and her nonprotein nitrogen level started to fall. We were confounded, however, when, after five days of diuresis, oliguria recurred. Cystoscopy at this time revealed that both ureters were occluded—and when ureteral catheters were passed, a profuse diuresis ensued and the nonprotein nitrogen level fell rapidly to normal. She was found to have benign strictures of both ureters and, although she never had fever, a large pyonephrosis on the right.

Dehydration

An extremely common sequence of events leading to deterioration of a patient with chronic renal disease is the vicious circle of dehydration. Decrease in extracellular fluids leads to a decrease in glomerular filtration and a diminution in urine flow.[5] This further diminishes the excretory efficiency of an already damaged kidney, the reserve of which is gone, that cannot produce a concentrated urine. Nitrogenous waste products and inorganic acids start to accumulate in the blood, and the patient becomes slightly nauseated and may vomit. This further depletes the extracellular fluid. This vicious circle can be set in motion by many things. The nocturnal obligatory polyuria of chronic nephritis can initiate morning dehydration with associated nausea. In many patients, a carbohydrate drink or a cup of hot milk or coffee immediately upon awakening is the best medicine to prevent

a bout of intractable vomiting. Ten to 25 mg. of chlorpromazine given on awakening and a half-hour before lunch will frequently prove useful in combating nausea. Although it is not entirely clear why patients with uremia become nauseated, the metabolic acidosis caused by the accumulation of sulfates and phosphates in body fluids undoubtedly plays an important role. Acidosis experimentally induced by various means regularly produces loss of appetite and nausea in normal subjects. The giving of appropriate amounts of sodium bicarbonate to a patient who has acidosis with renal insufficiency may restore his appetite and permit him to slake his thirst without vomiting. These patients tend to be exceptionally queasy. Because of the tendency of these patients to deteriorate rapidly, drugs that cause nausea must be used with caution. Similarly, hospital procedures that promote dehydration should not be employed. Witholding breakfast until blood is drawn at 10:00 or 10:30 a. m. or overnight dehydration for a concentration test may start a serious chain of events in a patient balanced on the brink of renal decompensation.

Because the patient with chronic nephritis is unable to produce a concentrated urine, he must excrete large amounts of urine in order to maintain a constant internal environment. Encouraging these patients to drink is, therefore, frequently the most important part of therapy. In patients who are not edematous this can best be done by the judicious administration of salt, preferably in salty foods or drinks. If pills of sodium chloride are prescribed, they should be taken with meals to minimize gastric irritation but must not be enteric-coated if absorption is to be assured. The salt has two functions. First, it stimulates thirst, increasing the intake and, hence, the output of fluids. Secondly, it replaces sodium lost in the urine in excessive amounts by patients with advanced nephritis.

Hyponatremia

In addition to the general decrease of body fluids associated with dehydration, an important cause of progressive uremia that can be successfully treated is hyponatremia, resulting from losses of sodium in excess of water.[6] Patients with damaged kidneys are especially prone to hyponatremia. When active reabsorption of sodium by the renal tubules is impaired, sodium may be "wasted" in the urine, even in the face of a falling level of serum sodium. "Salt-wasting" nephritis is, then, not a specific type of renal disease but rather a manifestation of renal insufficiency regardless of cause, in which the kidneys continue to excrete sodium without proper regard to the serum concentration of this ion.

In patients with or without underlying renal disease, the loss of gastrointestinal secretions by vomiting or diarrhea may be an important cause of sodium depletion. The loss of intestinal juices through draining fistulas or constant suction may produce large electrolyte deficits in surgical patients. During profuse sweating, as on the operating table, the loss of water and salt through the skin may attain significant proportions. The tendency to restrict salt in the postoperative period for fear of excessive salt retention has sometimes resulted in cases of salt depletion with resultant uremia. Replacement of fluid lost in such cases with parenterally given solutions containing no salt will restore extracellular fluid volume only at the cost of producing hyponatremia, hypotonicity, and overhydration of cells.

Sodium depletion may occasionally be produced by the injudicious use of mercurial diuretics in patients with congestive heart failure who are on a diet low in salt. And, occasionally, a patient with cirrhosis and ascites may develop signs of the "low-salt" syndrome when, after abdominal paracentesis, there is a rapid reaccumulation of ascitic fluid. If salt intake is restricted and these patients are allowed to satisfy their thirst with water at will, hyponatremia, circulatory collapse, and renal insufficiency may develop rapidly.

Regardless of how it is produced, severe hyponatremia per se profoundly disturbs the circulation and the function of the kidneys. Salt depletion tends to reduce cardiac activity and to lower arterial pressure. Rates of glomerular filtration and renal blood flow fall. Although the urine flow is usually reduced, uremia may develop with salt depletion even when the urine volume is normal. These patients are usually anoretic or nauseated and complain of great listlessness and fatigue. Painful muscle cramps are not uncommon. As sodium depletion progresses, they may become confused, somnolent, and comatose. The threshold for convulsions is lowered. Generalized muscular tremors and twitches may appear or, if already present, may grow worse. In fact, the neurological manifestations of hyponatremia may be the most striking symptoms of this condition and the most dramatically reversed with treatment.

Although the diseased kidney is particularly vulnerable to the effects of sodium deficits, hyponatremia can produce levels of nonprotein nitrogen of over 100 mg. per 100 cc. even in the absence of underlying renal disease. Urinalysis is usually of little help in differentiating the uremia of salt depletion and dehydration from that of primary renal disease. A low specific gravity, albuminuria, and formed elements in the urine may be present in both conditions.[7] The contribution of hyponatremia to renal insufficiency in a particular patient can, therefore, frequently be assessed only by correcting the hyponatremia.

In order to restore to normal the concentration of serum sodium, sodium must be administered in an amount necessary to restore osmotic concentration, not only in the extracellular space but throughout the total body water. If, then, the patient has a serum sodium level of 120 mEq. per liter and we want to give enough sodium to restore it to 135 mEq. per liter, we would need 135–120$\times$body water weight, in kilograms = 15$\times$60% of body weight in kilograms. In a patient weighing 70 kg., this would equal 15$\times$0.6$\times$70=15$\times$42=630 mEq. The sodium should be given intravenously in a minimum volume of water, as a 3 or 5% solution. If glucose in water is administered on the same day or if the patient is permitted to drink water or even to suck cracked ice, the effect of the hypertonic sodium chloride solution will obviously be nullified. For this reason, the giving of fluids should be restricted for a day or so after the hypertonic infusion is given. In any case, it is best to give reparative fluids in divided doses rather than all at once.

The response of a semicomatose patient to appropriate treatment is frequently striking. The patient awakens and

becomes responsive and alert. His blood pressure rises and urinary flow increases. The nonprotein nitrogen level begins to decline and may continue to fall for several days. In one man recently seen with chronic pyelonephritis, in whom the intravenous administration of calcium and heavy sedation with barbiturates had failed to relieve uncontrollable muscular tremors, correcting a serum sodium level of 115 mEq. per liter brought about dramatic relief from the tremors.

Unfortunately, not all patients can be expected to improve. Some patients with extensive pulmonary disease or other chronic wasting diseases seem to have chronic hyponatremia. In these people, a low level of serum sodium causes no symptoms; its correction is therefore without apparent benefit. In patients with severe intractable congestive heart failure, who are massively edematous and hyponatremic, the prognosis is usually poor. Although some do respond satisfactorily to the injection of sodium chloride solution, the majority do not. Their body fluids are merely diluted again and their edema increased when they are finally permitted to drink water.

TABLE 2.—*Data on Reversible Uremia Secondary to Calcium Ingestion in a Patient with Peptic Ulcer*

	5/17/55	5/25/55, 12 Gm. Calcium Daily	10/21/55, 1 Gm. Calcium Daily
Urine			
Specific gravity	1.022	1.009	1.015
Albumin level	0	1+	0
Sediment	0	2-4 white blood cells, 3-8 red blood cells	Occasional white blood cells, no red blood cells
Phenolsulfonphthalein excretion, %			
15 min.	25	5	20
Total	60	20	60
Blood			
Nonprotein nitrogen level, mg. per 100 cc.	39	143	38
Calcium, mg. per 100 cc.	..	16.5	10.7
Phosphorus, mg. per 100 cc.	..	5.8	4.4

Alkalosis and Potassium Depletion

Depletion of water and depletion of sodium are not the only correctable biochemical abnormalities that may produce reversible uremia. Chronic alkalosis as seen in patients with peptic ulcer who ingest enormous amounts of sodium bicarbonate may be associated with severe reversible disturbances in renal function.[8] The mechanisms involved are not completely understood. When alkalosis is induced and maintained over a period of days or weeks, there is a fall in glomerular filtration rate, an increase in nitrogen retention, a decrease in phenolsulfonphthalein excretion, and impairment of the ability of the kidneys to concentrate the urine. These functions slowly return to normal after the alkalosis is corrected. The effects of alkalosis may be due in part to a concomitant depletion of the body stores of potassium. Loss of body potassium is known to be harmful to the kidneys.[9] Rats kept on a low-potassium diet develop microscopic lesions in their kidneys and evidence of nitrogen retention. Inability to concentrate the urine and consequent polyuria are two of the first symptoms of experimental potassium depletion. Patients with chronic potassium depletion resulting from diarrhea may show renal and cardiac lesions at autopsy and during life may have a fixed urinary specific gravity that returns to normal when their potassium stores are repleted.

Patients with pyloric stenosis who vomit large quantities of acid stomach contents or habitually ingest enormous amounts of reabsorbable alkali demonstrate strikingly how alkalosis and potassium depletion can occur simultaneously, act synergistically to impair renal function, and act to perpetuate each other. Alkalosis per se tends to promote a greatly increased renal excretion of potassium. In association with a decrease in food intake resulting from vomiting, cellular stores of potassium can be seriously depleted. These patients may be admitted to the hospital dehydrated, with hyponatremia, alkalosis, low serum levels of chloride and high levels of bicarbonate, and with an elevated level of nonprotein nitrogen. Despite systemic alkalosis and dehydration, their urine is usually acid and of low and fixed specific gravity. It may contain albumin and casts. Correction of hyponatremia and of dehydration with sodium chloride solutions usually results in some improvement, but alkalosis and elevation of the blood urea nitrogen frequently persist until potassium salts are added to the repair solutions. Even then, although alkalosis rapidly disappears, renal function improves only slowly over a period of weeks and sometimes months. Patients in this state may have uremia fully as severe as that seen in the terminal stages of chronic glomerulonephritis, with complete recovery by the end of a year.

Hypercalcemia

A final fascinating and poorly understood cause of reversible renal insufficiency is hypercalcemia. Whether it be produced by hyperparathyroidism, by intoxication with vitamin D, by Boeck's sarcoid, or by the ingestion of massive amounts of milk and calcium salts, an elevated level of calcium in the serum appears to have peculiarly deleterious effects upon renal function. One mechanism responsible for the damage is, of course, the formation of stones, which lead to obstruction and infection of the lower urinary tract; another is the deposition of calcium in the collecting tubules, in distal tubular cells, and in the interstitial tissues of the kidney, producing the x-ray picture of diffuse nephrocalcinosis. But hypercalcemia may be associated with impaired renal function even in the absence of calcium deposition demonstrable either by x-ray studies or histologically.[10] A reliable physical sign of this condition is ocular calcification, best seen with a slit lamp, in the conjunctiva and cornea. In fact, such patients may complain bitterly of conjunctivitis. To the naked eye, the lesion of the cornea resembles arcus senilis, except that it is most prominent at the medial and lateral margins of the cornea rather than at the superior and inferior borders. When it is present, this lesion is diagnostic.

The loss of renal function associated with hyperparathyroidism or vitamin D intoxication may be very extensive. Deposits of calcium in the kidneys may produce permanent scarring and irreversible renal damage that may progress even though the hyperparathyroidism is cured or the patient stops taking vitamin D. When these advanced changes have not occurred, the improvement in renal function after, for example, parathyroid resection, may be dramatic. Hypercalcemia, renal calcification, and re-

sulting renal insufficiency are prominent features in some patients with Boeck's sarcoid. Treatment of such patients with cortisone may reverse the defect in calcium metabolism and produce a gratifying improvement in renal function.[11]

Patients with peptic ulcer who for years have ingested large amounts of milk, calcium carbonate, and calcium oxide (in the form of modified Sippy powders) may develop a syndrome consisting of an elevated level of serum calcium with normal levels of serum phosphorus and alkaline phosphatase and with metastatic calcification in the soft tissues, the eyes, and the kidneys. If a low-calcium diet is prescribed, there is slow regression of metastatic calcium deposits and improvement in renal function.[12] Occasionally, renal deterioration after a high-calcium diet may be astonishingly rapid, as in the following case.

CASE 3.—A 57-year-old diabetic man had had a duodenal ulcer for years. He was admitted to the hospital in May, 1955, because of recurrence of pain from an ulcer and at that time had reasonably good renal function, as indicated by a normal urinalysis, a high-normal level of nonprotein nitrogen in the blood, and a normal ability to excrete phenolsulfonphthalein dye. After eight days on a diet of calcium carbonate powders and milk and containing 12 gm. of calcium per day, he developed polyuria and became thirsty and stuporous. The level of nonprotein nitrogen had climbed to 143 mg. per 100 cc., and phenolsulfonphthalein excretion was seriously impaired. The urine showed albumin, red blood cells, and white blood cells, and the maximal specific gravity was 1.009. At this point the amount of serum calcium was measured and found to be greatly elevated, at a level of 16.5 mg. per 100 cc. Use of calcium was stopped and sodium chloride solution was infused. There was immediate improvement in his mental state and, at the end of three weeks, the nonprotein nitrogen level had fallen to a normal 36 mg. per 100 cc. Five months later, on a diet relatively low in calcium, the patient's serum calcium level and renal function had returned to normal (table 2). His condition presents an unusual and instructive example of renal insufficiency that proved reversible.

Summary

The prognosis in uremia is not necessarily hopeless. Treatable causes of renal impairment include congestive heart failure, dehydration, infection, obstruction, salt depletion, alkalosis, loss of potassium, and hypercalcemia. In addition, there are self-limited reversible causes of renal failure that, given time, may heal by themselves. Because of the nature of renal function, the rescue of a few nephrons and the salvage of a relatively small amount of renal function may make the difference between progressive deterioration with rapidly advancing uremia and renal compensation—with the addition of months and sometimes years of comfortable and useful life for a grateful patient.

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RADIOYTTRIUM (Y^{93}) FOR THE PALLIATIVE TREATMENT OF EFFUSIONS DUE TO MALIGNANCY

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• The effectiveness of intracavitary injections of Y^{90} in alleviating pleural and peritoneal effusions was tested in 16 patients with cancer. The effusion was completely halted in several cases, and the results were considered favorable in eight. In some the procedure as described did not halt the effusion, and in others the results proved difficult to evaluate.

Tracer studies showed that this isotope, a pure beta-emitter with half-life of only 61 hours, remained well confined to the serous cavity and was well distributed within it. The procedure was well tolerated. Neither early nor late side-reactions were observed.

Rapid fluid accumulation due to the involvement of the pleural and peritoneal cavities by malignant tumor presents a serious problem in the palliative management of patients with cancer. Radioyttrium (Y^{90}) seems to satisfy the requirements of intracavitary therapy with ionizing radiation. The material, simple to prepare and to administer, can be brought into intimate contact with the wall of the cavity upon which the intense beta rays of Y^{90} can exert their effect. The isotope is safe to handle, requires only moderate shielding, and presents no hazard to nursing and medical personnel.

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The yttrium oxide used in this study was supplied by Dr. Frank Spedding, Director, Ames Laboratory, Ames, Iowa.

The radioactive strontium-radioyttrium (Sr^{90}-Y^{90}) standard was supplied by Mr. Lou Stang, Chief, Hot Laboratory, Brookhaven National Laboratories.

Localization of Y^{90} in the injected cavity in the presence of sufficient yttrium carrier was previously reported from this laboratory.[1] Only small amounts of Y^{90} were found in the blood, urine, and stool and in the tissue samples assayed. This localization is probably due to the formation of colloids of yttrium with the constituents of fluid, principally with proteins. The small amount of yttrium that slowly escapes from the injected cavity into the circulation presents no significant danger to the patient, especially since the radioactivity decreases rapidly due to the 61-hour half-life of this isotope. The localization of Y^{90} was noted independently in experimental animals by Kyker [2] and in patients with cancer by Andrews and others.[3] Their radioautograms indicated deposition of yttrium on the serosal surfaces of the injected cavities.

Y^{90} has an additional advantage of safety for human therapy compared to other isotopes currently being employed. Whenever gaseous or liquid substances are introduced into body cavities, the danger of entry into the circulation exists. It is, therefore, important to survey the patient during the administration of the isotope. Should the isotope accidentally enter the circulation, a method is available for rapid removal of yttrium. If the calcium chelate of edathamil is immediately infused, chelated calcium will be exchanged for yttrium and substantial amounts of the newly formed Y^{90} chelate will be rapidly excreted by the kidneys.[4]

An exact evaluation of the therapy of pleural or peritoneal effusions caused by malignant tumor is rather difficult. There are a great many individual variations in the rate of fluid accumulation even in untreated patients. Also, the mechanism of fluid accumulation is not entirely understood. Animal studies suggest a correlation between the number of tumor cells and the amount of fluid formed. Goldie and Hahn [5] showed that the number of viable tumor cells was significantly reduced after the intraperitoneal injection of radioactive colloidal gold (Au^{198}) into mice with ascites caused by tumors. Similar results were obtained with radioactive lanthanum (La^{140}) and Y^{90}.[6] On the other hand, Andrews and others [7] observed a marked reduction of fluid formation after Au^{198} therapy, although tumor cells were present in a significant number of cases. The fact that fluid formation can decrease in spite of the persistence of tumor cells suggests that, in addition to the tumoricidal effects of ionizing radiation, fibrosis of the lining of the serous cavity, noted by Stembridge and others [8] and by us in the autopsy material of our series as described below, may be of importance. Some patients may continue to show significant fluid accumulation for several weeks after Au^{198} therapy and subsequently may still show a favorable response.[7] The same has been observed with respect to Y^{90} as described below.

Since good localization of Y^{90} was noted in normal and tumor-bearing animals and in patients with cancerous effusions,[1] it was decided to investigate the possible therapeutic usefulness of this isotope. Forty patients with cancer with effusions received tracer or therapeutic doses of Y^{90}. Blood levels and urinary and fecal excretions of the isotope and its toxicity were determined. The therapeutic effectiveness was investigated in 16 patients; the therapeutic results obtained in this small series seem to compare favorably with results obtained by other modalities of treatment.[7] The intracavitary administration of Y^{90}, therefore, may find its place in the palliative therapy of patients with cancer.

Materials and Methods

Preparation of Solutions.—At the Brookhaven National Laboratories, 250 mg. of yttrium oxide of high purity was irradiated in the reactor. The irradiated unit had a declared activity ranging from 50 to 125 mc. The radioactive yttrium oxide was dissolved in approximately 10 ml. of 1 *N* hydrochloric acid and brought to a volume of 25 ml. with sodium chloride solution. The solution was radioassayed against a Sr^{90}–Y^{90} standard making use of an aluminum absorber of sufficient thickness to absorb all of the beta rays of radioactive strontium (Sr^{90}). A suitable aliquot was withdrawn from the standardized stock solution into a flask containing 100 to 200 mg. of Y^{+++} as the chloride, and this solution was autoclaved.

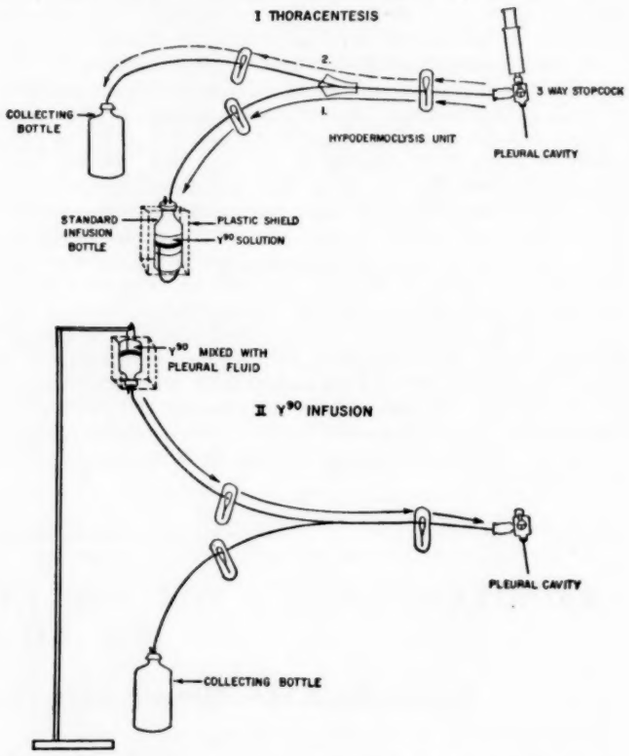

Fig. 1.—Method of intrapleural administration of radioyttrium (Y^{90}).

Method of Administration.—The method employed is illustrated in figure 1. In intrapleural administration, a no. 14 polyethylene catheter was introduced into the pleural space and was connected by a hypodermoclysis set with two glass flasks so that a closed system was established. Approximately 100 ml. of aspirated chest fluid was first delivered into the Lucite-shielded flask, which already contained 100 ml. of sterile sodium chloride solution, the prepared Y^{90} solution, and 1 ml. of heparin. (The addition of protein-containing fluid to the isotope solution generally results in the formation of a finely dispersed suspension. It seems desirable to ensure uniform distribution of the isotope in a relatively large volume of fluid outside the body, thus minimizing local precipitation at the time of injection.) This flask was gently agitated as the pleural fluid was added. The remainder of the aspirate

was delivered through the other arm of the Y-shaped hypodermoclysis unit into the second glass flask. The flask containing the isotope was then suspended from a standard and the contents allowed to flow into the cavity. The puncture site was closed upon removal of the polyethylene tube by means of a preplaced purse-string suture.

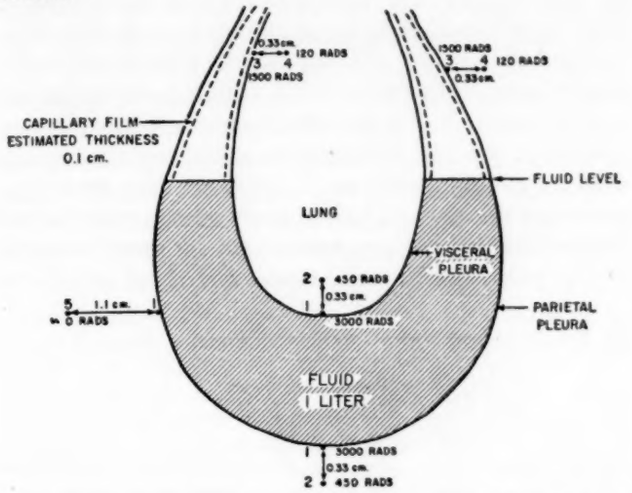

Fig. 2.—Diagram of integrated radiation dose delivered to the walls of a pleural cavity after an injection of 30 mc. of radioyttrium (Y^{90}). The cumulative dose was estimated on the assumption that, after thoracentesis, about 1,000 ml. of fluid remains. A rad is a unit of absorbed radiation dose equal to 100 ergs per gram and is approximately 1.08 rep.

In intraperitoneal administration, after introduction of the polyethylene tube and removal of 100 ml. of ascites fluid for mixture with the isotope solution, abdominal paracentesis was performed at another site in the routine manner. Upon its completion, the puncture site was closed and the isotope solution was infused through the polyethylene tube, as described above.

After the isotope was given, the patient was placed on an oscillating bed for one hour to attempt uniform distribution of the isotope in the injected cavity. During the instillation of Y^{90}, the probe of a survey meter was held in the patient's hand. If accidental entry into the circulation had been detected, the infusion could have been discontinued and appropriate measures taken. Should Y^{90} accidentally enter the circulation, immediate intravenous infusion of the calcium chelate of edathamil is advised. It is suggested that 5 ml. of a 20% solution of calcium edathamil be injected for three to five minutes and be followed by an intravenous drip of 500 ml. of 5% dextrose in water containing 20 ml. of a 20% solution of calcium edathamil over a period of four hours.[4]

Sample Preparation and Counting.—One to 2 ml. of liquid samples—blood, urine, or serous fluids—was pipetted into small metal planchets. The samples were dried under an infrared lamp and counted with an end-window tube. Experimental standards were similarly prepared, and the results obtained were expressed as a percentage of the dose administered. When dried liquid samples were counted, no significant error due to self-absorption was noted.

Calculation of Radiation Dose

Yttrium ^{90} is a pure beta emitter with a maximum energy of 2.2 mev. and a maximum tissue range of 1.1 cm. Its half-life is 61 hours. The radiation delivered to the walls of a pleural cavity after an injection of 30 mc. of Y^{90} has been estimated on the assumption that after thoracentesis about 1,000 ml. of fluid remains. The cumulative dose delivered to various sites is diagramed in figure 2. It should be noted that the strong 2.2 mev. beta rays of Y^{90} result in a considerable radiation dose at the surface and to a depth of about 3 mm., while the radiation at greater depths rapidly declines to negligible values. Once the isotope has been infused, and barring leakage from the cavity, there is no apparent radiation damage sustained by distant tissues and little hazard to nursing and medical personnel.

Results

Studies on Distribution and Excretion.—Tracer or therapeutic doses of Y^{90}, with 100 to 200 mg. of stable yttrium as the carrier, were injected into the pleural or peritoneal cavity of 40 patients with cancerous effusions. After the administration of Y^{90}, samples of blood and daily urine and fecal collections were radioassayed, in some cases for as long as 19 days. In addition, Y^{90} concentrations were determined in samples of fluid from the injected and, whenever possible, from the uninjected cavities. Several needle biopsy specimens of bone and liver were also assayed. The results of these studies are illustrated by one representative example.

A 25-year-old male had a reticulum cell sarcoma with extensive abdominal node involvement, ascites, and bilateral pleural effusions. He had received x-ray therapy to several abdominal portals and sterile mechlorethamine hydrochloride (nitrogen mustard) was administered intravenously, with only slight improvement. In spite of this treatment, repeated aspirations of abdominal and pleural fluid were necessary to relieve distressing symptoms. On Oct. 5, 1954, a dose of 9.5 mc. of Y^{90} with 120 mg. of Y^{+++} as the carrier was instilled into the right pleural cavity. Radioassays were performed on plasma, urine, and stool specimens; fluid from both pleural cavities; ascites; and needle

TABLE 1.—*Distribution of Y^{90} After Intracavitary Administration, Yttrium Content as a Percentage of Dose Administered**

Time, Day	In 1 Ml. Plasma	In 24 Hr. Urine	In Stool Collection	Other Samples
30 min.	0.000007	.....	.....	
1	0.00002	0.027	0.001	
2	.....	0.041	0.009	
3	0.00002	0.036	.....	
4	.....	0.041	.....	
5	.....	0.048	0.007	
6	0.00001	0.041	0.001	Bone biopsy: 0.00022%/gm.†
7	.....	0.042	.....	Liver biopsy: 0.0009%/gm.‡ Aspiration from uninjected pleural cavity: 0.00003%/ml. Paracentesis: 0.000005%/ml.
8	0.00002	0.050	.....	
9	.....	0.040	0.014	
10	0.00001	0.050	.....	Aspiration from injected pleural cavity: 0.012%/ml.
11	.....	0.050	.....	
12	.....	0.046	0.016	
13	0.00001	0.049	.....	
14	.....	0.041	0.006	
15	0.00002	0.038	.....	
16	.....	0.039	.....	Aspiration from injected pleural cavity: 0.007%/ml.
		Total 0.679	Total 0.054	

* Case 8, table 2.

† Needle biopsy from the iliac crest. Assuming a skeletal mass of 15% of body weight and uniform distribution, the yttrium content is estimated to be 2.2%.

‡ Assuming a liver weight of 1.5 kg., the yttrium content is estimated to be 1.4%.

biopsy specimens of liver and of bone obtained from the iliac crest. The values are listed in table 1. The blood drawn 30 minutes after the intrapleural instillation of yttrium showed only very slight but detectable radioactivity of 0.000007% per milliliter of plasma; 24 hours later the activity was 0.00002% per milliliter of plasma and stayed within this range throughout the 15-day period of observation. Multiplying these values by the estimated total plasma volume, the yttrium present in the plasma of this patient ranged from 0.02 to 0.06% of the administered dose. The daily urinary excretions (column 3, table 1) were rather low and ranged from 0.027 to 0.050%; the cumulative urinary excretion in 16 days was 0.679% of the administered dose. The fecal excretion (column 4, table 1) was even lower, the cumulative excretion being 0.054% in 14 days. On the seventh day, samples were obtained from the uninjected left pleural cavity and from the abdominal cavity; the yttrium concentrations in these samples were very low and were comparable to those in the plasma. The yttrium concentration, however, in samples aspirated from the injected pleural cavity on the 10th and 16th day after the instillation of Y^{90} was 1,200 and 350 times higher than in the plasma. The assays of samples of bone and liver taken one week after the administration of the therapeutic dose suggest an approximate uptake in bone of 2% and in liver of 1.4%. These biopsy results are very approximate, since they are based upon assays of very small samples and on estimated organ weights and assume homogeneous distribution of the yttrium.

It can be concluded from these data that no significant radioactivity was present in the blood at any time and that the excretions were very low. Furthermore, fluid samples obtained from two uninjected cavities contained insignificant amounts of yttrium, whereas those from the injected cavity were considerably richer in yttrium. The low uptake in liver and skeleton is in agreement with the data on localization of the isotope in the injected cavity. Similar results were obtained on other patients so studied.

Therapeutic Results.—As for patient material and follow-up, 16 patients are included in this series, 13 receiving Y^{90} intrapleurally and 3 intraperitoneally. In all but one patient (case 11, table 2), the diagnosis of malignancy was established microscopically. The tumorous nature of effusions was proved prior to the yttrium therapy in 12 patients. The recurrence of effusions in the remaining three patients strongly suggested malignancy as the etiology. An attempt was made to select patients for this therapy who required repeated aspirations of fluid; for instance, eight thoracenteses were performed in a period of four and one-half months with removal of a total of approximately 8,100 ml. of fluid from the patient in case 2, table 2. On the other hand, the patient in case 7, table 2, was also accepted for this therapy, since she required two thoracenteses of 1,900 ml. each during the preceding nine days. The frequency of aspiration and the amounts of fluid removed after treatment were compared to the pretreatment period and served as criteria in gauging the effectiveness of therapy. Although the estimation of the rate of fluid accumulation was attempted roentgenographically, it was abandoned except to estimate the amount of fluid present immediately after the administration of yttrium and at the end of the follow-up period. In cases in which an autopsy was performed, the fluid remaining in the injected cavity was measured.

The dose administered and data relating to the therapeutic evaluation of patients receiving Y^{90} intrapleurally are presented in table 2. Seven of the 13 patients appear to have derived benefit from this therapy, 6 of these requiring no further thoracenteses during a follow-up period at least as long as the pretreatment period of observation. In three of these six patients, no fluid could be detected at the end of the follow-up period (cases 1, 4, and 7); in two patients (cases 2 and 6) the fluid estimated to be present at the end of the follow-up period was less than that remaining in the cavity at the time of yttrium

TABLE 2.—*Effect of Intracavitary Administration of Y^{90} on Accumulation of Pleural Fluid*

			Before Y^{90} Instillation, Fluid Removal			Instillation of Y^{90}		After Y^{90} Instillation, Fluid Removal					
Case, No.	Diagnosis	Tumor Cells in Fluid	On Days	Total Vol., Ml.	Fluid Remaining, Ml.*	Date	Dose, Mc.	On Days	Total Vol. Ml.	Follow-Up Period, Days	Fluid Remaining, Ml.†	Status of Patients	Final Evaluation
1	Carcinoma of breast	—	1, 6, 14, 30, 55	2,700	0	10/27/54	10	0	0	197	0	Ambulatory, at home	Good
2	Carcinoma of lung	+	1, 7, 14, 25, 87, 109, 123, 133	8,100	2,000 1,500	11/20/54 12/16/54	10 20	.. 0	.. 0	... 137	.. 600+	Died 5/2/55	Good
3	Carcinoma of lung	+	1, 15, 29	4,300	1,000	12/16/54	30	8	2,350	82	800	Died 3/8/55	Good
4	Carcinoma of lung	+	1, 4, 54, 78	3,600	2,000	1/ 6/55	30	0	0	128	0	Ambulatory, at home	Good
5	Carcinoma of rectosigmoid	+	1, 5	3,430	1,000	2/ 1/55	29.5	0	0	44	2,000	Died 3/17/55	Good
6	Carcinoma of lung	—	1, 22, 38	2,000	500	2/17/55	32	0	0	86	300	Hospitalized for hemoptysis, no respiratory symptoms	Good
7	Carcinoma of breast	—	1, 9	3,800	500	2/18/55	18	0	0	85	0	Ambulatory, at home	Good
8	Reticulum cell sarcoma	+	1, 54	4,000	0	10/ 5/54	9.5	21	3,000	73	0	Died 12/17/54	Questionable decrease
9	Carcinoma of breast	+	1, 87	1,250	1,500	10/ 5/54	9.5	128	700	219	1,500	Ambulatory, at home	Questionable decrease
10	Primary unknown	+	1, 20, 53, 62	5,425	500	3/ 1/55	29.5	17, 24	3,105	75	500	Hospitalized for congestive heart failure	Questionable decrease
11	Malignant thymoma	—	1, 21, 58, 71, 129	12,150	300	11/20/54	9.6	0	0	68	1,500‡	Died 1/27/55	Indeterminate
12	Carcinoma of esophagus	+	1, 12, 16	6,650	300 800	12/21/54 1/ 6/55	10 20	.. 11, 22, 35	.. 7,500	... 48	.. 500‡	Died 2/23/55	Failure
13	Carcinoma of lung	+	1, 13	2,700	800	2/ 1/55	30	15, 36	3,400	49	700‡	Died 3/22/55	Failure

* At time of Y^{90} instillation. † At end of follow-up, volume estimated on the basis of roentgenograms. ‡ Measured at autopsy.

instillation; one patient (case 3), who was considered improved after the therapy, required one thoracentesis eight days after the instillation of yttrium and none during the subsequent two months. At death, 800 ml. of fluid was estimated to be present. In three patients, the therapeutic benefit was only suggestive. The patient in case 8 required one thoracentesis three weeks after the instillation of yttrium. When he died 52 days later, no fluid was estimated to be present in the chest cavity. The patient in case 9 required one thoracentesis in the seven months after treatment; she is ambulatory and at home. This patient, however, needed only two thoracenteses during the three months prior to therapy. The patient in case 10 seemed to have a slower rate of fluid accumulation after the yttrium therapy than before. The patients in cases 12 and 13 did not improve. The patient in case 11 requires more detailed comment.

The patient, a 71-year-old, who was admitted because of marked dyspnea, left pleural effusion, and x-ray evidence of a mass in the mediastinum. Obstruction of the superior vena cava was proved. In spite of extensive investigation, which included bronchoscopy, biopsy, and repeated examinations of the sputum and of pleural fluid for tumor cells, no histological diagnosis of tumor could be established. X-ray therapy to the mediastinum relieved the superior vena cava obstruction only partially and temporarily but did not affect the accumulation of chest fluid. Shortly thereafter, 9.6 mc. of Y^{90} was instilled into the left pleural cavity. This was followed by marked relief of the respiratory distress. Five thoracenteses had to be performed in the four months prior to therapy, with removal of 12 liters of fluid, whereas after administration of Y^{90} there was no need for thoracentesis up to the time of the patient's death 68 days later. During this time, the obstruction of the superior vena cava persisted. On postmortem examination, a malignant thymoma, with extensive involvement of the mediastinum, including the pericardium, was found. The visceral and parietal pleura, however, were free of tumor. For this reason, and in spite of the apparent benefit that this patient derived from the treatment, he was not included in the series of patients considered improved by Y^{90} therapy.

Three patients received Y^{90} intraperitoneally: the first patient so treated received 10 mc.; the other two patients received 30 and 40 mc. respectively. Two patients died too soon for therapeutic evaluation. The third patient, who had carcinoma of the breast with peritoneal carcinomatosis, required paracenteses at approximately three-week intervals in the 10 months preceding yttrium therapy. Only one paracentesis was required three weeks after the instillation of 40 mc. of Y^{90} into the peritoneal cavity, at which time 2,500 ml. was removed, and no paracentesis has been necessary for four months. She is ambulatory, at home, and considerably improved.

To summarize the therapeutic results in the 16 patients included in this series: in 8 patients there was good control of fluid; in 3 there was a slight or questionable decrease; in 2 there was no improvement; in one results were indeterminate; and in 2 results could not be evaluated because death occurred too early.

Clinical Side-Reactions and Autopsy Findings.—In order to insure close observation during and after the administration of Y^{90}, all patients were hospitalized, most of them for several weeks. The clinical observations were supplemented by laboratory studies that included roentgenograms prior to therapy, immediately after instillation of yttrium, and at least once a week subsequently. Repeated complete blood cell counts, including platelet counts and bone marrow aspirations, were performed. No side-reactions attributable to stable yttrium were noted; no symptoms of radiation sickness were observed; no depression of the hematopoietic system was detected in any of the patients. In several instances, transient chest pain was noted after the instillation of yttrium. Autopsies were performed on five patients; in four of these, thickening of the pleura in varying degrees was found. Fibrous adhesions and loculation of fluid were present in one patient. No radiation damage to the lungs, to adjacent organs, or to the bone marrow was noticed.

Summary and Conclusions

Radioyttrium (Y^{90}), a beta-emitting isotope of relatively short half-life, was administered intracavitarily to patients with cancer with pleural and peritoneal effusions. Tracer experiments showed that this isotope remained well localized in the injected cavity in the presence of the stable yttrium carrier. The therapeutic effectiveness was tested in 16 patients. Favorable results were obtained in eight patients. The procedure was well tolerated, and neither early nor late side-reactions were observed. The advantages of this intracavitary therapy are the favorable radiation characteristics of this isotope and the increased safety to patients and to personnel. These advantages and the therapeutic results suggest that this modality of treatment may find its place in the palliative management of cancer.

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Nonpenetrating Abdominal Trauma.—Improvement in the mortality in patients with abdominal trauma will depend on (1) earlier admittance to the hospital, (2) rapid restoration of blood loss, (3) early exploration on the basis of reasonable suspicion of isolated intra-abdominal injury, (4) careful evaluation of abdomen in presence of multiple injuries, (5) use of modern restorative vascular techniques, (6) vigorous treatment of air passages in associated chest injuries, and (7) appropriate antibiotic and electrolyte therapy.—G. V. Pontius, B. C. Kilbourne, and E. G. Paul, Nonpenetrating Abdominal Trauma, *A. M. A. Archives of Surgery*, May, 1956.

CANCER OF THE THYROID AND IRRADIATION

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• *The amount of radiation that reaches the thyroid during x-ray treatments for benign hyperplasia of the nasopharynx was measured. The customary three treatments, with a total of 375 r to each of two lateral fields, resulted in a maximum of 18 r reaching the skin above the thyroid over a period of two weeks. This is much less than the amount of radiation that reaches the thyroid during the usual fluoroscopic examination of the chest.*

This study concerns 25 patients under the age of 21 who had been referred for treatment of carcinoma of the thyroid during the past 18 years. Of these, only four had had previous irradiation. On the other hand, during the same 18 years, 2,500 children received radiation therapy for hypertrophic lymphoid tissue in the pharynx and for enlarged tonsils, and 480 of these upon examination were found not to afford a single instance of carcinoma during a follow-up period of 7 years.

In a report on carcinoma of the thyroid by Dwight Clark,[1] it is strongly suggested that an association exists between the increasing frequency of carcinoma of the thyroid in children and their previous exposure to irradiation for treatment of benign lesions in the head and neck area. Specifically indicted are previous treatments with x-rays of enlarged tonsils and hypertrophic lymphoid tissue in the pharynx and x-ray therapy to the thymus; this latter implication is seemingly confirmed by other reports in the literature. Clark's published paper and his presentations before medical societies have found their way into the lay press, where they have been interpreted as proof of an actual correlation between radiation therapy and subsequent cancer development in the thyroid of children. The same interpretation has been accepted by large segments of the medical profession, especially by pediatricians responsible for the recommendation of radiation therapy for the above-mentioned pathological conditions. It therefore appears appropriate to investigate such allegations of cause and effect on the basis of present knowledge and experience.

Reports in the Literature

Clark reports the observation of 13 children (12 girls, 1 boy) with carcinoma of the thyroid who at one time or another previous to the establishment of the diagnosis had received x-ray therapy to the head, neck, or upper chest areas; 5 received treatments for enlarged tonsils (2 of these also for adenoids), 3 for enlarged thymus, 3 for cervical adenitis, one for sinusitis and peribronchitis, and one for pertussis. It is assumed that a relation exists between the development of cancer and the amount of radiation given (more than 200 r) and with the time between irradiation and the appearance of the malignancy (average 6.9 years). As corroborating evidence, Duffy and Fitzgerald [2] are quoted; in 1950 they reported 28 children with carcinoma of the thyroid who were observed at the Memorial Hospital in New York, 10 of whom were found to have had received previous irradiation of the thymus. It might be stated at this point that their summary contains the brief statement "ten of the cases received radiation for 'enlarged thymus' between the fourth and sixteenth months of life," but in the text of their report they stated: "To propose a cause-and-effect relationship between thymic irradiation and the development of cancer would be quite unjustified on the basis of data at hand when one considers the large number of children who have had irradiation to an 'enlarged thymus.' However, the potential carcinogenic effects of irradiation are becoming increasingly apparent, and such relationship as those of thymic irradiation in early life and the subsequent development of thyroid or thymic tumors might be profitably explored."

From the Tumor Clinic of Michael Reese Hospital.

Read before the winter meeting of the Central Society of Nuclear Medicine, Chicago, Feb. 12, 1956.

Three other pertinent papers should be mentioned here; they were published by Dailey and Lindsay [3] on thyroid neoplasms in youth in 1950, by Horn and Ravdin [4] in 1951 on carcinoma of the thyroid gland in youth, and by Warren, Alvizouri, and Colcock [5] in 1953 on the same subject, and describe entirely different experiences. Dailey and Lindsay report 23 carcinomas of the thyroid in patients under 20 years of age without mentioning any previous irradiation. Horn and Ravdin specifically state, "In our series we have noted no familial histories of thyroid disease; nor a history of previous radiation therapy for thymic enlargement, as was the case in ten of Duffy's and Fitzgerald's patients." Warren and his co-workers did not find any significant etiological factors in their series of 23 patients in the age group under 20 and declared, "While it has been suggested that the prophylactic irradiation of the thymus may be a factor in the etiology of thyroid carcinoma, our experience, perhaps inadequate, makes this seem unlikely. One patient in our series, and only one reported other than by Duffy, received irradiation of the thymus before the development of thyroid carcinoma." In a study reported in 1948 by Conti and Patton [6] on 7,391 newborn infants, no carcinoma of the thyroid was reported in the 1,477 patients of this group who had received x-ray therapy.

Simpson, Hempelmann, and Fuller [7] reported that, in a follow-up study of 1,400 children in a group of 1,722 treated for thymic enlargement, 17 children were found to have developed malignancies, 6 of which were carcinoma of the thyroid. While this was a significantly higher incidence than that observed among the untreated siblings of the children who had received irradiation and in the general population, the authors also stated: "A considerable number of siblings were excluded from the series because they were alleged to have had x-ray therapy," and, "It must also be noted that the incidence of cancer among the untreated siblings is high compared with the general population."

Analysis of Reported Findings

These abstracts from the literature indicate that the above-mentioned authors either specifically eliminated irradiation as a precursor in the development of thyroid cancer in children, or, in instances where x-ray treatments had been previously administered, they commented on this incidence with considerable restraint. Of 28 children with carcinoma of the thyroid reported by Duffy and Fitzgerald, only 10 had had previous irradiation, while of 68 children (23 seen by Dailey and Lindsay; 22 by Horn and Ravdin; and 23 by Warren and Alvizouri), only one had had x-ray therapy.

While no attempt is made to explain or to suggest how cancer of the thyroid is produced or initiated by irradiation, certain statements purporting to suggest such correlation can easily be refuted. As evidence of the increasing frequency with which cancer of the thyroid is observed in children, Winship [8] in 1952 published statistics revealing that, from 1930 to 1935, 12 new carcinomas of the thyroid in children were reported; from 1936 to 1940, 18 were reported; from 1941 to 1945, 30 were reported; and from 1946 to 1950, 91 were reported.

From these figures, the increasing number of reported cases of carcinoma of the thyroid in children is evident. Clark assumes and states that this rise in the observation of thyroid carcinoma in children corresponds to the number of children exposed to therapeutic radiation to the head and neck area. This assumption is not supported by facts. Actually, irradiation of the tonsils and adenoid tissue was first proposed by Regaud in 1913, and the original report in the American literature was published in 1920 by Witherbee. There followed a paper by Witherbee in 1924,[9] one by Watkins [10] in 1924, another by MacCready [11] in 1925, and others. Some of these papers were published after presentation at medical society meetings, and from the published discussions it is evident that in the years between 1920 and 1925 this form of treatment was quite popular and widely used. Undoubtedly many hundreds of children were treated during these years and probably many thousands. If it were correct that a relation exists between irradiation and development of cancer of the thyroid in children, an increase should have been evident in the 5 and 10 years following the widespread application of such radiation therapy. Actually, less than 10 cases of cancer of the thyroid in children were reported between 1925 and 1930 and only 12 between 1930 and 1935.

Another point worth mentioning is the distribution of carcinoma of the thyroid between the two sexes. In adults a numerical relation of seven carcinomas of the thyroid in females to one in males is generally accepted. Such a drastic difference in the sex distribution does not seem to prevail in children; however, the preferential affliction with carcinoma of the thyroid of girls is an established fact. Since the benign conditions for which radiation therapy to the head and neck area in children are customarily given do not show any sex preference, and since both sexes have been exposed to this form of therapy in almost equal numbers, one might expect a change in the sex ratio of carcinoma of the thyroid in children if there were any correlation between irradiation and cancer development in this organ. No such evidence has been reported.

It must also be taken into consideration that x-ray treatments for assumed benign conditions in the neck area may have been given to children at a time when unrecognized carcinoma of the thyroid was present. An illustrative observation may be cited: A 12-year-old girl was referred to the tumor clinic for treatment of adenoid tissue in the pharynx and enlarged lymph nodes in the neck because, as the referring physician explained, the child had failed to show any response to x-ray therapy administered approximately two months earlier. The lymphadenopathy was of such nature that an "aberrant thyroid syndrome" was suspected, and biopsy of the lymph nodes revealed presence of metastatic carcinoma of the thyroid. Similar observations were also made at Michael Reese Hospital in two other instances, and the perseverance of lymph nodes in the neck area that eventually proved to be carcinoma of the thyroid is confirmed in the literature. Warren and Alvizouri reported six patients in their group who had had masses in the neck since birth. Duffy and Fitzgerald state that "all cases showed lymph nodes or thyroid nodules present for months to years, that were later proven to contain carcinoma." Obviously, carcinoma of the thyroid in children is often present for years without producing sufficient symptoms to warrant consultation or treatment. It appears entirely feasible that some children received radiation therapy for assumed benign lesions at a time when they actually were suffering from carcinoma of the thyroid; therefore, a correlation between the two events might easily be construed wrongly.

In trying to explore whether a relation between the application of ionizing radiation and development of carcinoma of the thyroid exists, it appears significant that in animals cancer of the thyroid has never been produced with x-rays. In 1952, Goldberg and Chaikoff [12] reported the experimental inducement of carcinoma of the thyroid in 9 out of 25 rats following application of radioactive iodine in combination with thiouracil. However, no attempt has been made to correlate such experiments in rats with human pathology.

Present Study

It must appear of considerable interest to ascertain the amount of radiation that is applied to the region of the thyroid when children are exposed to x-ray treatments for benign lesions. I have carried out measurements during radiation therapy of hypertrophic lymphoid tissue in the pharynx and tonsils and found that, if the customary three treatments with 200 kv. (constant potential) and a total of 375 r to each of two lateral 8-by-10-cm. fields were applied, the total radiation reaching the skin above the thyroid amounted to a maximum of 18 r over a period of two weeks. Since most of the exposure of this area is due to stray radiation, the actual amount reaching the thyroid is, of course, less. This figure of a maximum of 18 r in itself may mean little to the average reader. However, it becomes more significant when compared with the amount applied with other uses of ionizing radiation. Measurements taken during x-ray examinations of children in the diagnostic x-ray department indicate that, during fluoroscopy of a child's chest in the posterior-anterior position under routine conditions, the skin over

the thyroid receives 1 r within five minutes; however, the posterior portion of the neck under the same condition receives 18 r each minute. It can easily be shown that, if a child is exposed for a few minutes and rotated in front of the fluoroscopic screen, the amount of radiation absorbed in the thyroid area during fluoroscopic examinations of the chest is much greater than that applied to the same area during therapeutic use for benign conditions. Since fluoroscopic examinations of the chest in children are done by the thousands daily, one would reasonably assume there to be a much higher incidence of thyroid carcinoma in children if the alleged correlation existed. Conversely, one might again wrongly draw the logical conclusion to refrain from further use of x-rays for fluoroscopy of the chest in children.

My own observations regarding carcinoma of the thyroid in children have been presented on various occasions on the basis of different age groups. In this study all patients with carcinoma of the thyroid up to and including those 20 years old who were referred to the department for treatment during the past 18 years will be described. The number of patients totaled 25; of these, 4 had had previous irradiation. One of these four was 10 years old at the time carcinoma of the thyroid was diagnosed and had received x-ray therapy to the tonsils more than eight years prior to the establishment of the diagnosis outside of our hospital. No record, however, is available, and the parents did not remember the exact time of treatment, the number of exposures, or the name of the physician. In the second child, the interval between radiation therapy of the tonsils, which was administered in our department, and the establishment of the diagnosis of carcinoma was nine years. The third patient had received x-ray treatments in 1939. In October, 1950, 11 years after treatment of the tonsils, the patient was seen in consultation for enlarged lymph nodes in the neck; immediate biopsy was advised but was not performed until January, 1951. At that time histological studies revealed a papillary adenoma in "accessory thyroid tissue." Surgery of the thyroid gland was advised but not carried out because the patient appeared to be symptom-free. However, surgery was performed three years later, in January, 1954, and the diagnosis of an adenocarcinoma in the right lobe of the thyroid was established. In the fourth patient, the time interval between x-ray therapy of the tonsils and the establishment of the diagnosis of carcinoma of the thyroid was 15 years.

A fifth patient is not recorded here because she belongs to the previously mentioned group, in whom the diagnosis of carcinoma of the thyroid was missed. This case was originally diagnosed as tuberculous cervical adenitis, since unilateral lymphadenopathy had been noticed for at least one year and calcification in the nodes was present. X-ray therapy was administered in 1944 and 1947 without benefit; at the time of surgery, in 1947, five months after the last treatment, carcinoma of the thyroid with metastases to the chain of lymph nodes was found.

The time intervals between irradiation and establishment of the diagnosis of malignancy in the four reported patients were more than 8 years, 9 years, 14 years, and 15 years respectively. It might be mentioned that in this group of 25 patients it was found that in two instances siblings of patients with malignancy had received irradiation and remained well, whereas the untreated children developed carcinoma.

Our records indicate that approximately 2,500 children received radiation therapy of hypertrophic lymphoid tissue in the pharynx and enlarged tonsils during the last 18 years; of these, the response to the treatments was evaluated in 600 patients treated between February, 1938, and December, 1942, and the findings were published in 1948.[13] In 480 patients of this group who were observed in cooperation with an experienced pediatrician and an ear, nose, and throat specialist, not a single instance of development of carcinoma was found during the follow-up period, covering up to seven years. The three patients with carcinoma of the thyroid who were treated at the Michael Reese Hospital belong to this group and developed carcinoma after the reported time intervals. Another patient who also belongs to this group eventually developed carcinoma of the thyroid and was reported by Clark, who performed the surgery. It is true that all of the 2,500 cases have not been evaluated as yet. However, I believe that the facts reported here are of considerable value because the referring pediatricians have had excellent follow-up records on their patients and have often proved to have more correct information on previous treatments and other data than the parents of these children.

Comment

In an attempt to explain the increasing incidence of carcinoma of the thyroid in children, I have tried to consider every possible factor. One might, of course, question the accuracy of the statistical reports. But, even considering the fact that a number of solitary observations of carcinoma of the thyroid may not be reported in the literature, I believe that there is sufficient reason to assume that the published statistics accurately reflect a true increase in carcinoma of the thyroid in children during the last 10 to 15 years. A similar increase in the incidence of cancer of other organs has been reported, the best example being bronchiogenic carcinoma.

An important question is whether cancer in human beings can be directly produced or initiated by the action of ionizing radiation. If we exclude the few instances of bone tumors following permanent application of radioactive substances and other rather rare tumors of the larynx and ovary, our main observations are confined to the skin. Cancer of the skin has developed in an appreciable number of patients following the overadministration of x-rays or radium. In all these instances primary reactions of the skin had been noticed a short time after irradiation, though the cancer itself might not have developed for many years thereafter. Without going into detail regarding the development of cancer in the injured skin, it may be stated that, as far as can be ascertained, not a single instance is known where less than 1,500 r had been applied to the area of later cancer development. In the overwhelming majority of these patients, the amount of radiation was more than 5,000 r. In such instances, the histological picture of the carcinoma and its surrounding tissue has shown characteristic changes that can be attributed to the effects of ionizing radiation. In

no instance of carcinoma of the thyroid in children who had received previous radiation were such or similar changes found.

Another point to be considered is the attempted correlation on a statistical basis. The mere fact that two variables are significantly correlated does not in itself prove that the correlation has any biological meaning. If a relatively small number of lesions of a certain pathology is found in patients who had been subjected to common procedures, it is very easy to construe a correlation. To my knowledge, injections of antidiphtheria serum have never been accused of being responsible for the development of malignancies that are common in children, as for example retinoblastomas, Wilms' tumors, or cerebellar tumors. It would undoubtedly be easy to construe such a correlation on a statistical basis.

Duffy and Fitzgerald considered the possibility of a correlation of cancer of the thyroid in children and the beginning of puberty. They also mentioned the onset of one thyroid tumor and the acceleration of another during pregnancy and suggested that a complex endocrine influence might be operating in at least some cases of thyroid carcinoma. These observations raise the question of whether the same unknown agent that is responsible for the enlargement of the thymus might also be able to produce an enlargement of the thyroid and subsequently cancer in susceptible patients. It is known that tumors can develop in endocrine glands without the presence of a cancerogenic agent. Hypofunction or hyperfunction of one endocrine organ can set in motion a chronic disturbance of the secretory and growth equilibrium, which may eventuate in tumor formation in a functionally related endocrine organ. Estrogen was the first hormone so incriminated, but it now appears that an excess of thyrotropic hormones or the absence or insufficiency of thyroid hormones may act as a specific growth stimulus, leading under certain circumstances to development of tumors in the thyroid, ovary, or pituitary gland. These hormones are ordinarily not thought to be carcinogenic agents, and it is at present purely speculative as to how, if the equilibrium in the target is not restored, abnormal growth is induced.

If the pro and con of cause-and-effect of irradiation and development of carcinoma of the thyroid in children are evaluated, the following conclusions are obvious: The fact that some children who developed carcinoma of the thyroid had at one time or another previously received x-ray therapy to the head and neck area is no proof that a correlation between the two events exists. The reasons why such a correlation appears to be unfounded have been discussed elsewhere herein. Numerically, many more cases of cancer of the thyroid have been reported in children who did not receive irradiation than in those who were exposed to such treatments. Numerous theoretical possibilities of association have not been discussed here because they appear to be just as speculative as the alleged correlation with irradiation. The only important conclusion that we can draw is the necessity of carefully evaluating conditions of all children and adolescents observed with carcinoma of the thyroid for possible clues of causal genetic possibilities.

Summary

A careful review of the pertinent literature and my own observations of 25 children exposed to irradiation and of children and adolescents with carcinoma of the thyroid do not justify the acceptance of a correlation between radiation therapy and the increased frequency of carcinoma of the thyroid in youth. The assumption that the rise in carcinoma of the thyroid corresponds to the number of children exposed to therapeutic radiation is not corroborated by facts. It could be shown that in some instances children had unrecognized carcinoma at the time they received treatments with x-rays. The amount of radiation applied to the thyroid area in common therapeutic procedures is smaller than that absorbed during chest fluoroscopy. Statistically, the correlation of irradiation and development of carcinoma of the thyroid is untenable.

29th Street and Ellis Avenue.

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Cardiac Rupture.—It appears that the incidence of cardiac rupture has increased with the advent of anticoagulants. The latest figures collected by Wright and his associates show that the incidence of this complication is 2.4 per cent in untreated cases and 4.1 per cent in the treated group. We must therefore assume that almost 2 per cent of patients who received anticoagulants in the course of an acute infarction will die from cardiac rupture associated with the therapy. Often it is not a through and through rupture but only a seepage of blood between dissected layers of myocardium. If signs of cardiac tamponade appear, aspiration of blood from the pericardial sac may be lifesaving; discontinuation of the anticoagulant and administration of counteracting agents is of course mandatory. Even complete rupture of the heart may not be fatal. We once saw the post mortem of a patient whose heart had a hole the size of a nickel which was covered by a thick pericardium adherent to the muscle. Histologic examination revealed the complete absence of muscle fibers over this area. The clinical data and the histological findings indicated that this patient had survived the perforation of the heart muscle for some time. The presence of pericardial thickening and of adhesions may explain why perforation is so rarely the cause of death even when very large cardiac aneurysms are present.—D. Scherf, M.D., Of What Do Heart Patients Die? *Transactions of the American College of Cardiology*, April, 1955.

HEPATIC PATHOLOGY IN JAUNDICE DUE TO CHLORPROMAZINE

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• *Jaundice in four patients who had received chlorpromazine was observed under conditions that afforded a unique opportunity for the study of hepatic alterations. In one, a biopsy was done. In the other three, autopsies were performed after death from other causes. The hepatic tissues formed a series manifesting chlorpromazine jaundice in various stages of its development and recession.*

During the jaundice there was intrahepatic canalicular obstruction indistinguishable from other types of obstructive jaundice except those in which the larger bile ducts were markedly involved, usually as a result of extrahepatic duct obstruction. After recession of the jaundice the liver tissues apparently returned to normal without residual evidence of injury.

The findings suggested the likelihood that chlorpromazine caused an increased viscosity of the bile leading to stasis in the smaller bile passages.

Although the development of jaundice in patients receiving chlorpromazine has been seen repeatedly,[1] there have been only limited observations on the changes that occur in the liver in this condition, and these have been made chiefly on tissues obtained by needle biopsy.[2] Autopsy findings in patients who have died while jaundiced, or shortly after jaundice had cleared, have not been described in detail. The pathological changes in the liver therefore require further study.

Recently four cases of jaundice due to chlorpromazine have come under our observation under conditions that have afforded a unique opportunity for the study of the hepatic alterations. Briefly, two patients who had received chlorpromazine died while jaundiced and autopsy was done. A third patient, who had received chlorpromazine and had been icteric for about one month, had an exploratory laparotomy performed while the jaundice was at its height, and a generous biopsy of the liver was obtained. A fourth patient, who had had chlorpromazine jaundice for five weeks, died approximately one week after clinical icterus had disappeared and also came to autopsy. The hepatic changes found in each of these cases, together with a brief clinical history, are presented below.

Report of Cases

CASE 1.—This 50-year-old man was admitted to the hospital because of headache and personality changes that had followed a minor head injury. Neurological studies led to the diagnosis of a possible intracranial lesion, and craniotomy 10 days after admission disclosed a neoplasm in the left temporoparietal region of the brain. A portion of the tumor was removed and proved histologically to be an astrocytoma, grade 4 (glioblastoma multiforme). After the operation some improvement was observed and the patient was discharged to a nursing home. Nine weeks later, because of signs and symptoms suggesting a recurrence of the neoplasm, he was again admitted to the hospital. Therapy with chlorpromazine, 25 mg. daily, was started on the fifth hospital day. Five weeks later jaundice was noted and use of the drug was discontinued. The liver was not enlarged or tender. Bile was present in the urine, and the stools were acholic. Other significant laboratory findings are recorded in the table. The patient died on the 67th hospital day, approximately 28 days after the institution of chlorpromazine therapy. At this time the scalp over the region of the craniotomy was bulging and the skin surfaces generally were deeply jaundiced.

At autopsy the liver was greenish brown, smooth, of average consistency, and weighed 1,260 gm. The cut surfaces had a mottled appearance somewhat resembling that of chronic passive congestion. The striking histological features were the prominent central pigmentation of the hepatic lobules and the mild degenerative changes in numbers of the central hepatic cells. Two types of pigment were present in the central portions of the lobules. One of these was dark brown, amorphous, and of semifluid consistency and was obviously bile. It occurred chiefly in distended intercellular canaliculi but was present also in small numbers of hepatic cells that showed mild parenchymatous degenerative changes and in many Kupffer cells in the central and midzonal regions. The changes were obviously those of quite marked bile stasis that was localized rather strikingly to the central portions of the lobules.

The second pigment, found especially in the central hepatic cells but also in smaller quantities in many Kupffer cells, was finely granular, golden brown, and very different from the more homogeneous bile pigment. It was not hemosiderin, as shown by special tests, but resembled the finely granular, yellowish pigment seen in the central hepatic cells in a variety of unrelated conditions. Although these degenerative changes, with the associated pigment deposits, extended to the midzonal portions of the lobules, there was little evidence of degeneration, abnormal pigmentation, or bile stasis in the peripheral portions of the lobules. The portal areas showed little of note. They were lightly infiltrated by inflammatory cells, chiefly lymphocytes, but these were of nonspecific type. The bile ducts and ductules were not abnormal and showed no evidence of bile stasis. At autopsy the gallbladder and the extrahepatic bile ducts showed no evidence of mechanical obstruction. Other major anatomic findings were recurrent astrocytoma, grade 4 (glioblastoma multiforme), involving the left temporoparietal region of the brain; marked edema and congestion of the brain; and bile nephrosis.

CASE 2.—This 51-year-old white man had had psoriasis for 30 years. Because of nervous tension he was given 25 mg. of chlorpromazine three times daily. Grippe-like symptoms appeared on the 16th day; on the 17th day he became nauseated and vomited and stopped taking the drug. Icterus appeared on the 19th day. The presumptive diagnosis was infectious hepatitis, and he was treated at home. After four and a half weeks of unremitting icterus, the patient was admitted to the hospital. On the basis of certain laboratory tests (see table), the icterus appeared to be of obstructive type, and an exploratory laparotomy was performed to determine the cause. No gross obstruction was found, but a liver biopsy was done. Two weeks after admission, 25 mg. of cortisone three times daily was administered. During the next two days there was a notable reduction in jaundice, the patient himself reported an improvement in his general well-being, and there was a precipitous fall in the serum bilirubin level. The patient continued to improve.

The histological changes in the liver of this patient were identical with those found in the liver of the patient in case 1 and need not be described again. At the time of laparotomy the liver, according to the surgeon, was rather small, with a smooth sur-

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face, somewhat greenish, and quite firm. The gallbladder and the extrahepatic bile ducts appeared normal, and careful examination failed to reveal any organic biliary obstruction.

CASE 3.—A 53-year-old man, known to have had hypertension for eight years, was admitted to the hospital because of anuria,

Results of Laboratory Studies in Four Patients with Jaundice Due to Chlorpromazine

Case and Date	Bilirubin Total, Mg./ 100 Ml.	Bilirubin Direct, Mg./ 100 Ml.	Thymol Turbidity, Un[its]/ 100 Ml.	Alkaline Phosphatase, Units/ 100 Ml.	Prothrombin, % of Normal
Case 1					
12/27/54	0.4	...	2.6	...	..
2/ 2/55	9.0	5.2	3.9	...	70
2/ 7/55	14.6	9.5	1.3	1.8	..
2/ 9/55	...	...	...	...	45
2/26/55	16.5	...	1.3	...	50
Case 2					
3/21/55	20.0	13.0	1.3	2.1	85
3/24/55	19.5	10.6	...	1.7	..
3/28/55	20.0	...	...	...	..
4/ 2/55	24.6	...	...	...	..
4/ 4/55	14.4	9.4	...	...	..
4/12/55	10.0	5.3	...	...	..
5/13/55	1.8	0.8	...	...	..
Case 3					
12/28/54	2.6	1.8	...	...	..
Case 4					
2/15/55	9.9	6.1	2.6	...	..
2/18/55	13.2	9.1	...	...	..
2/25/55	21.0	6.5	...	...	..
3/ 1/55	14.7	8.8	...	...	..
3/ 3/55	...	...	...	2.7	..
3/16/55	2.2	1.2	...	...	..
3/21/55	...	...	...	3.5	..
Normal range	0.2-0.8	0-0.2	0-4.7	0.5-1.5	..

persistent nausea and vomiting, and slight icterus. He had received 25 mg. of chlorpromazine four times daily for 15 days immediately prior to admission and continued to receive 25 mg.

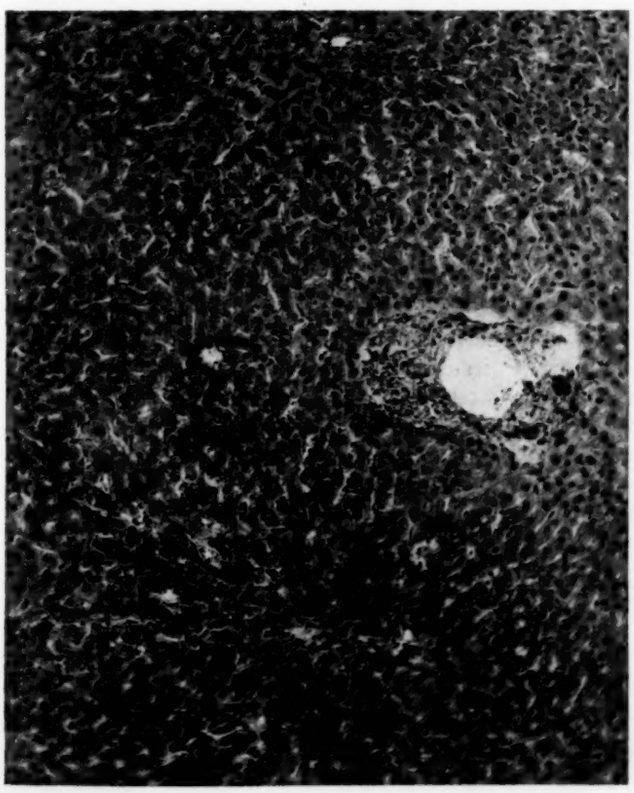

Fig. 1 (case 2).—Low-power photomicrograph showing localization of intrahepatic biliary obstruction and pigment deposit in central zones. The portal regions and the hepatic tissues about them are not involved (× 94).

three times a day for the first 2 hospital days, after which use of the drug was discontinued. Since his complaints were believed to be primarily due to advanced renal disease, all therapeutic measures were directed toward the improvement of his cardiorenal status. The nonprotein nitrogen level rose progressively to

Fig. 2 (case 2).—High-power photomicrograph of hepatic tissue in central portion of lobule showing bile stasis in intercellular canaliculi and pigment deposits in hepatic cells and enlarged Kupffer cells (× 469).

312 mg. per 100 ml. and the creatinine to 20 mg. per 100 ml. Whenever blood samples were drawn, the serum was recorded as icteric. The patient was still slightly jaundiced when he died in uremia on the 11th hospital day.

On gross examination the liver was pea green, smooth, and of normal outline. It weighed 1,700 gm. Its exposed surfaces showed prominent lobular markings not unlike those seen in chronic passive congestion. On histological examination numbers of cells in the central portions of the lobules showed parenchymatous degenerative changes, and, as in the other two cases, two types of pigment were present in these regions. These pigments resembled those found in the livers of the patients in cases 1 and 2, and their distribution was similar. The only difference was that in the liver of this patient the quantities of the pigments, especially the bile pigment, were somewhat less, especially in the liver cells themselves and in the intercellular bile canaliculi. Except for the presence of small numbers of lymphocytes, which were scattered irregularly throughout the stroma, the portal areas were not remarkable.

At autopsy the gallbladder and the extrahepatic biliary system were carefully explored but failed to reveal any evidence of mechanical obstruction. The other important anatomic findings were advanced arteriolar nephrosclerosis, marked hypertrophy of the left ventricular myocardium, acute pulmonary edema, and acute hemorrhagic pancreatitis involving chiefly the body and tail of the organ.

CASE 4.—Because of recent personality changes, this 84-year-old woman, known to have had diabetes mellitus for 10 years, received 25 mg. of chlorpromazine three times daily for 10 days. She was then referred to a psychiatrist, who continued to administer the drug but increased the dosage to 50 mg. four times daily. On the 12th day of chlorpromazine therapy, the urine was dark brown and the stools were light yellow. The next day the patient was obviously jaundiced. Use of the drug was discon-

tinued, and she was admitted to the hospital for study. During the first 10 days the jaundice continued to deepen but then gradually diminished in intensity until it finally disappeared (see table for laboratory data). However, arteriosclerotic gangrene of the right foot developed, the diabetes mellitus and the electrolyte balance became difficult to control, and death occurred on the 48th hospital day, approximately a week after the disappearance of clinical jaundice.

At autopsy the liver was normal in color, shape, and consistency. It was somewhat small, weighing 1,220 gm. On section the lobular pattern seemed to be slightly exaggerated, but little else was observed. Histologically, a few hepatic cells in the centers of the lobules and small numbers of Kupffer cells in the immediate neighborhood were found to contain varying, and usually small, amounts of finely granular, brownish pigment in their cytoplasm, but there was only the slightest trace of bile stasis in the form of minute accumulations of bile pigment in a few hepatic or Kupffer cells or in intercellular canaliculi. There were no evidences of scarring, abnormal bile duct proliferation, or other alterations indicative of permanent hepatic damage. Slight, very early acute central hepatic necrosis was present, but this was unquestionably a terminal event unrelated to chlorpromazine therapy.

Although carefully examined, the gallbladder and the entire extrahepatic bile duct system showed no evidence of mechanical obstruction. The other important anatomic findings were histological changes compatible with diabetes mellitus, generalized advanced arteriosclerosis, arteriosclerotic gangrene of the right lower leg and foot, moderate hypertrophy of the left ventricular myocardium wih focal cardiosclerosis, bilateral basal bronchopneumonia, and toxic nephrosis.

Comment

The hepatic tissues in these four cases provided an unusual opportunity to study the pathological changes that may be associated with chlorpromazine jaundice in various stages of its development. In cases 1 and 2 the changes were those present when the jaundice was at its height and were primarily those of central degeneration of the liver cells, with bile stasis and local pigment deposits similar to those present in cases of moderately severe obstructive jaundice. In case 3 the severity of the changes had diminished somewhat and resembled those occurring during the clinical resolution of obstructive jaundice. In case 4 the jaundice had disappeared and the liver showed minimal changes, little more than vestiges of the changes found in the active stages of the condition, showing that little or no permanent damage is done to the liver itself.

During the time that the patient was actually icteric while receiving chlorpromazine therapy, the changes observed were similar to those found in obstructive jaundice and were characterized by marked pigmentation of the central hepatic cells and the neighboring Kupffer cells, distention of the intercellular canaliculi by bile, and focal degenerative changes in the central hepatic cells. Minimal inflammatory cell infiltrations of the portal areas were sometimes present, but their relationship to therapy with chlorpromazine was less clear.

When the histopathological changes found in the livers of these patients were compared with those observed at autopsy in cases of extrahepatic obstruction of the biliary tree, no absolute distinguishing features could be recognized unless the extrahepatic obstruction was so marked as to result in marked stasis in the major ducts in the portal areas as well. Special staining techniques, including the periodic acid–Schiff stain and Van Giesen, Giemsa, and Verhoeff stains, also failed to disclose any specific changes characteristic of chlorpromazine injury that might differentiate this form of hepatic damage from that found in other types of biliary obstruction.

Cases 3 and 4 represented stages in the resolution and termination of the hepatic changes. The findings would appear to indicate that there was virtually complete restoration of the normal hepatic pattern following the recession of jaundice. No regions of scarring, no evidences of cirrhosis, and no evidences of bile duct proliferation remained, and there was no histological evidence of any residual or continuing hepatic cell injury. The early acute central hepatic necrosis observed in case 4 was undoubtedly a terminal event unrelated to administration of the drug.

The mechanism by which intrahepatic bile obstruction developed in chlorpromazine jaundice was not altogether clear. The changes suggested that something prevented the bile from leaving the central portions of the hepatic lobules and reaching the larger ducts in the portal areas. The result was bile stasis, which was most striking in the central regions of the lobules. It was clear in all four cases that extrahepatic biliary obstruction was not the underlying cause.

An interesting, and possibly a significant, clinical finding was the almost dramatic clearing of the jaundice in case 2 after the administration of cortisone. The reason for this effect was not altogether clear, but one may speculate as to the possible cause. Recently Patterson and his associates [3] have shown that the administration of cortisone can have two kinds of effects on bile and bile flow. It can lead to an increased volume flow (hydrocholeresis) as well as to an increase in the concentration of bilirubin and bile salts in the bile itself (choleresis). Since the giving of cortisone to one of these patients was followed by a sudden fall in serum bilirubin level and marked reduction in the degree of clinical jaundice, it would appear that, in the absence of detectable mechanical obstruction, the cortisone in some way affected the bile itself, especially the bile that had been congested in the bile canaliculi, leading to its mobilization and release. This would suggest that chlorpromazine might produce its effect in the liver by causing some alteration in the composition of the bile that would result in its increased viscosity, or actual inspissation, thus leading to stasis in the small, centrally placed canaliculi, with ensuing regurgitation of bile into the circulating blood. Indeed, it is possible that the phenomenon may not be unlike that occurring in certain types of so-called inspissated bile syndrome in children.[4] If this thesis were true, the effect of cortisone would be to reduce the viscosity of the bile trapped in the finer bile channels, thus permitting it to flow into the larger ducts.

Summary

The hepatic tissues from four patients who became jaundiced while receiving chlorpromazine therapy showed intrahepatic bile canaliculus obstruction that was indistinguishable from other types of obstructive jaundice except those in which the larger bile ducts were markedly involved, usually as a result of extrahepatic duct obstruction. After the recession of the jaundice the liver tissues apparently returned to normal without residual evi-

dence of previous injury. The markedly icteric patient from whose liver a biopsy specimen was taken responded well to cortisone therapy. The three other patients died—one while intensely jaundiced, one while jaundice was receding, and the third after jaundice had disappeared. Autopsy was done in these cases. Though the mechanism by which jaundice is produced in these cases is not yet fully clear, it is suggested that chlorpromazine may directly affect the liver in such a way as to alter the composition of the bile, leading to its inspissation or increased viscosity. The resulting increase in viscosity could lead to intrahepatic bile stasis, especially in the smaller canaliculi.

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2. Footnote 1*c-f*.

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CHRONIC POSTHERPETIC NEURALGIA

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• *The course of postherpetic neuralgia was studied in 35 patients, some of whom had suffered severely for more than three years. All of the patients were over 40 years of age. The sexes were almost equally affected. The thoracic nerves were involved most frequently, and the trigeminal nerves next.*

Five patients with trigeminal involvement were treated with thiamine hydrochloride, nicotinic acid, tincture of belladonna, and phenobarbital, but only one was benefited. Six patients with involvement of the thoracic nerves were treated with the same medication, with significant improvement lasting several months in one case. Intradermal injections of procaine or saline solution, peripheral neurectomies, procaine and alcohol blocks, skin excision, skin undercutting, roentgen ray therapy, posterior rhizotomy, chordotomy, lobotomy, spinal anesthesia, intrathecally administered alcohol, and paravertebral sympathetic block by means of procaine gave varied results.

This experience has led to a policy of selecting a surgical operation with low morbidity as the initial step and proceeding to another if the first fails.

Considerable advances have been made in the control of various types of intractable pain, yet postherpetic neuralgia remains singularly unresponsive to the armamentarium of pain-relieving drugs and surgical procedures. It is because there is no satisfactory treatment that so little has been written on this subject. Nevertheless, certain procedures have been found helpful at times, and, therefore, we have felt it was time to discuss the problem again and to record the experiences that we have had with this condition at the Lahey Clinic over the past 20 years.

Clinical Picture

The pain associated with herpes zoster is the most important symptom and usually is first noticed with the onset of the rash but may precede it. It starts with a burning discomfort and hypersensitivity of the skin in the involved dermatomes. In severe cases the pain is continuous even when the skin is not touched. The pressure of clothing or any movement that pulls or stimulates the skin aggravates the pain and often evokes lancinating stabs of pain. Usually the pain diminishes after the eruption has appeared, and, by the time the skin has healed, only slight tenderness of the area is still present.

Certain patients, however, are less fortunate. Even when the skin in the involved area has become irregularly scarred and pigmented, the constant day and night pain does not subside. Examination reveals sensory disturbances, with the dermatome hyperesthetic or anesthetic, although usually the scarred spots are anesthetic and the intervening skin hyperesthetic. Pinprick, heat, and cold are often not felt until fairly intense but then produce a very disagreeable spreading, burning pain similar to that associated with peripheral nerve injuries and with central pain like that of the thalamic syndrome.

As time goes on, the pain persists rather than diminishes. The patients' physicians try all the known medicaments for pain relief and find none that are more than temporarily beneficial. The patients become distraught and discouraged, and their frustrated physicians become convinced that the disorder is functional or "psychogenic." The neurosurgeon is called upon to help control the pain and finds that the standard procedures for dividing the pain pathways to the involved area are not always successful in relieving the patient. This is the picture of severe, intractable, postherpetic neuralgia with which this paper is concerned.

Analysis

The present study is based on the case histories of 35 patients treated for chronic postherpetic neuralgia during the past 20 years. We were interested to note whether there were any common factors among those developing postherpetic sequelae and those who did not. The following points were noted in our series.

From the Department of Neurosurgery, the Lahey Clinic.

Age.—Age is a distinct factor inasmuch as herpes zoster affects patients in all age groups, yet postherpetic neuralgia seldom, if ever, appears before the fourth decade. In our series the average age was 62.3 years; all patients were over 40, and 75% were between 60 and 80 years of age.

Sex.—Herpes zoster affects both sexes almost equally, and postherpetic neuralgia develops in similar proportion (males, 14, or 40%, and females, 21, or 60%). Sex, therefore, did not seem to be an influencing factor.

Zone of Distribution.—The cutaneous zones involved in postherpetic neuralgia were likewise in the same proportion as in acute herpes. The thoracic nerves were affected most frequently, the trigeminal nerves next, and the lumbar, cervical, and sacral areas less commonly.

Physical Condition.—Most patients were elderly, so hypertension and arteriosclerosis were prevalent concomitant findings, but the patients were not otherwise in poor general health. Eight of the 35 patients had some other major illness.

Psychological Status.—Psychological status was a difficult aspect to evaluate, as it was often impossible to separate patients who were nervous wrecks before the development of herpes zoster from those whose emotional symptoms began only after the neuralgia had started. We were impressed with the number of patients who were quite stoic individuals, and we found very few whose symptoms were not confined to their herpetic sequelae.

Duration of Symptoms.—Sixty-eight per cent of the patients, when first seen by us, had had symptoms for over a year and 39%, for more than three years. This not only stresses the chronicity of postherpetic neuralgia but emphasizes that it is usually a well-fixed pain problem when first encountered by the neurosurgeon.

Pathophysiology

It has long been evident that the intractable postherpetic pain was not a simple peripheral neuralgia, and it has been assumed, of course, that knowledge of the pathological mechanisms involved would point the way to the logical therapeutic approach. At the present time we do not know the full sequence of events that occurs when postherpetic neuralgia develops, but many writers have contributed to our understanding of the process. We might summarize the current concept something like this: The process starts with an elderly patient who has an acute and usually a severe attack of herpes zoster. The herpes virus produces pathological lesions chiefly in the dorsal root ganglions of the spinal nerves and their homologue of the cranial nerves. Areas of inflammation and degeneration can also be observed in the nerve trunks, spinal cord, and skin. The cutaneous inflammatory foci that implicate nervous structures may be present months after the acute attack. Browder and de Veer [1] have emphasized that these foci would seem to be adequate cause for the persistence of pain throughout this period.

Of the entire group affected, the neuralgia does not persist in those patients who are young, those with mild attacks, and those who secure adequate pain relief at the outset, but, in patients in the elderly age group with a lowered tolerance to pain, in whom the burning, aching, and boring discomfort does not diminish for many weeks, a new process occurs. The sustained and excessive bombardment of the pain pathways sets up a central disturbance within the nervous system so that self-perpetuating circuits are established and a central pain syndrome is formed. Sugar and Bucy [2] have pointed out the similarity to the thalamic syndrome and believe that this change occurs at the thalamic level. The process is facilitated by the presence of cerebral arteriosclerosis with its associated mild hypoxia that lowers the threshold at the synapses. Pain impulses relayed to the cortex, instead of becoming dispersed, might then be able to continue around the corticothalamic circuits, restimulating the thalamus and reinstituting pain. Livingston [3] has thought that the establishment of a vicious circle is a characteristic response of the nervous system to chronic pain and that a similar mechanism occurs in phantom limb causalgia, atypical facial neuralgia, and other forms of protracted pain. In any event, once the vicious circle has been set up, the central process becomes the chief disturbance so that, even when the painful area that initiates the process is removed, other stimuli may be able to sustain the pathological mechanism.

Results of Treatment for Postherpetic Neuralgia Involving the Trigeminal Area

Medical Management.—As the type of pain involving the trigeminal area is chronic and continuous, narcotics are contraindicated because of addiction liability. Nonnarcotic analgesics are helpful but usually afford insufficient relief. We usually give in addition a therapy consisting of thiamine hydrochloride, nicotinic acid, tincture of belladonna, and phenobarbital. Of five patients given this therapy (table 1), one was helped so that no surgical procedure was necessary; the other four were not significantly benefited. Psychotherapy in the form of reassurance and encouragement is extremely important in the management of this condition, because most patients are despondent and discouraged. Nielsen [4] has had some success with cobra venom, and others advise repeated administration of intravenously given procaine.

Intradermally Administered Procaine. — Procaine given intradermally was used on one patient. Almost complete relief of pain was obtained for about a year, and six intradermal injections kept him comfortable for a seven-year period.

Procaine and Alcohol Nerve Blocks.—In one patient procaine nerve block was done three times, following which she was considerably improved for one and a half years. A second patient experienced no relief of pain from procaine nerve block despite resultant skin anesthesia. An infraorbital nerve block using alcohol gave one patient two months' relief. A second patient had no benefit.

Peripheral Neurectomies.—One patient had six supraorbital neurectomies, after each of which she obtained considerable improvement, lasting about two years. Two patients were temporarily relieved for a few months. A fourth patient had pain in all three trigeminal divisions; an infraorbital neurectomy gave relief in that area but the third division pain seemed more intense, and it

was necessary to divide this branch. Complete relief occurred for three months, followed by persistent local soreness of the tissues. Poppen [5] has pointed out that neurectomies may help when the dermatome is hyperesthetic but are of no value when the skin is anesthetic.

Skin Excision.—Skin excision has been tried in supraorbital herpes (see figure). A crescent-shaped area of supraorbital skin is excised, and the edges are brought into apposition after mobilization of the skin along the borders. This usually includes excision of any scar tissue and nerve elements down to the periosteum. We used this method on three occasions when the patients had become refractive to local blocks and neurectomies. Each time significant improvement lasting several months. However, it was noticeably helpful as an adjunct to other procedures and was usually given for a period after various surgical procedures and nerve blocks. In addition, some of the patients had received multivitamins; high does of thiamine (vitamin B_1), cyanocobalamin (vitamin B_{12}), or ascorbic acid (vitamin C); chlorpromazine (Thorazine); cortisone; and physiotherapy, including diathermy and heat lamps. None showed more than mild improvement at the start of the therapy.

X-Ray Treatment.—Although x-ray treatment to the spinal ganglions has been useful in acute herpes, we have not found it to be of much value in treating postherpetic neuralgia. Of eight patients given x-ray therapy, six were not helped. One was improved to a moderate extent but was also receiving medical treatment. Another patient had relatively mild symptoms, and after x-ray therapy she was able to tolerate the residual discomfort without needing any additional procedures.

TABLE 1.—*Results of Treatment for Postherpetic Neuralgia Involving the Trigeminal Area*

Treatment	No. of Patients	Improvement: Marked: Years	Improvement: Marked: Wk. to Mo.	Improvement: Moderate: Years	Improvement: Moderate: Wk. to Mo.	Improvement: Little or None
Medical	5	..	..	1	..	4
Intradermally given procaine	1	1	..	..	..	..
Procaine nerve block	2	1	..	..	..	1
Alcohol nerve block	2	..	1	..	1	1
Peripheral neurectomy	4	..	2	1	1	..
Skin excision	2	2	..	..	..	..
Total	16 *	4	3	2	2	6

* The survey was made on six patients with involvement of the trigeminal nerve but, as many had several different procedures, table shows their individual response to these different treatments and gives a total figure of 16. In no instance was complete relief obtained.

TABLE 2.—*Results of Treatment for Postherpetic Neuralgia Involving the Spinal Dermatomes*

Treatment	No. of Patients	Complete Relief	Improvement: Marked: Years	Improvement: Marked: Wk. to Mo.	Improvement: Moderate: Years	Improvement: Moderate: Wk. to Mo.	Improvement: Little or None
Medical	6	..	..	..	..	1	5
X-ray	8	..	..	..	1	1	6
Intradermally given procaine	13	..	2	6	..	..	5
Intradermally given saline solution	1	..	..	1	..	..	..
Intercostal procaine block	9	..	..	..	..	1	8
Intercostal alcohol block	1	..	..	..	..	..	1
Posterior rhizotomy	4	1	1	1	..	1	..
Skin excision	5	..	1	..	3	..	1
Skin undercutting	2	..	1	..	..	1	..
Chordotomy	1	..	..	..	..	1	..
Prefrontal lobotomy	1	..	..	..	1	..	..
Spinal anesthesia	3	..	..	..	..	1	2
Intrathecally given alcohol	1	..	..	..	..	..	1
Sympathetic block	1	..	..	..	..	..	1
Total	56 *	1	5	8	5	7	30

* The survey was made on 29 patients with spinal nerve involvement, but, as many had several different procedures, table shows their individual response to these different treatments and gives a total figure of 56.

Intradermally Administered Procaine.—Five patients were relieved for only an hour or two when given procaine intradermally. Six patients had relief from a few weeks to several months, and in two patients the neuralgia was completely controlled over the years by widely spaced intradermal injections.

Intradermally Administered Saline Solution.—Intradermally given solution was used on only one occasion, they obtained considerable improvement for an average of two years. Poppen [5] prefers to turn a typical right frontal flap, reflecting it on a subcutaneous plane down to the surpraorbital border where the nerves and vessels are excised.

Other procedures that have been reported in the literature but not used at this clinic include retrogasserian neurectomy, alcohol injection of the gasserian ganglion, stellate ganglion block, and cervical sympathectomy.[3]

Results of Treatment for Postherpetic Neuralgia Involving the Spinal Nerves

Medical Management.—The neuralgia therapy, as mentioned previously, was used on six patients with involvement of the thoracic area (table 2). Only one had

and it gave effective relief for several weeks. This patient had received intradermally given procaine, and the results with saline solution were comparable.

Intercostal Procaine and Alcohol Blocks.—Southworth and Hingson [6] reported excellent relief with procaine nerve blocks for herpetic pain during the early stages. We treated nine patients with chronic postherpetic pain, and no prolonged periods of improvement were afforded. One was improved for several weeks, three were benefited for a few hours, and four did not experience even temporary relief. Intercostal alcohol block was tried in only one patient and did not alleviate the symptoms.

Posterior Rhizotomy.—Four patients were treated by posterior rhizotomy. The first patient continued to have pain above the denervated area, but a second rhizotomy gave complete relief. The second patient obtained marked improvement (80 to 90%) and no further treatment was

Method of combining peripheral neurectomy with skin excision in treatment of postherpetic neuralgia involving supraorbital area.

necessary. The third individual complained of pain above and below the anesthetic area, and it was necessary to perform a skin excision at a later date. The fourth was temporarily relieved, but the pain gradually returned and eventually reached its previous intensity. We believe, as does Hyndman,[7] that, in patients whose pain is confined to a comparatively narrow band (three or four intercostal nerves), posterior rhizotomy may be successful if carried out two segments above and below the involved area.

Skin Excision.—Browder and de Veer [1] have advocated excision of the skin of the involved dermatomes and described several successes. We found that after this procedure patients often retained some pain along the incisional line with soreness on pressure around the excised area. The extent to which these residual symptoms bothered the patient determined the result. One patient believed he had obtained about 85% relief. Three others believed they were relieved about 40%, and the fifth said she was no better, although her relatives thought she was improved inasmuch as she required less medication and complained to a lesser extent.

Skin Undercutting.—Abbott and Martin [8] have described subdermal denervation for postherpetic neuralgia. One of our patients had skin excision of the central area with the adjacent margins undercut for 4 or 5 in., and he obtained 80 to 90% relief. In the second patient this was a last resort procedure after countless other measures had failed. He was better immediately after operation, but several weeks later the pain had become reestablished.

Chordotomy.—Some patients are reported to have been relieved by chordotomy but, as Kahn [9] pointed out, usually it is unsuccessful. In our series it was performed on one patient after spinal anesthesia had afforded complete temporary relief. He obtained freedom from pain for two weeks, then his symptoms gradually returned to their former intensity.

Lobotomy.—Prefrontal lobotomy can alter the patient's reaction to his psychic and peripheral irritants, thus effecting relief from the vicious pain cycle, as Falconer's [10] successful case indicates. We used it on only one patient who had had postherpetic neuralgia for 15 years and after all other procedures had failed. A unilateral lobotomy was first tried, and the patient became less tense but showed no alteration of his pain response. Four months later the other side was done, and, as before, the patient said its severity was unchanged. He was observed to be less disturbed by it but was not thought to have been satisfactorily relieved.

Spinal Anesthesia.—Two patients were not relieved in the least by spinal anesthesia; the third was relieved for one month the first time and obtained only temporary relief on the next two occasions. On the third occasion the patient said he was relieved about 20% during the time the anesthetic level was above the painful dermatomes.

Intrathecally Administered Alcohol.—Alcohol, given intrathecally, was used twice on one patient and no relief was obtained.

Paravertebral Sympathetic Block (Procaine).—Several authors [11] have reported success with sympathetic block in alleviating acute herpetic discomfort, but it has seldom been useful in helping patients with postherpetic neuralgia. We used it on one patient whose pain was confined to the leg (fifth lumbar and first sacral area) and found that, although the leg became warm after the block, the pain remained unaltered.

Summary and Conclusions

Of all the pain syndromes encountered in medical practice, postherpetic neuralgia is one of the most difficult to treat. Its occurrence is confined to patients past middle age. It is seldom helped by any medicine, and it seldom improves as time goes on. Often it has been present several years when first encountered by the neurosurgeon. The pathophysiology is not proved, but it is known that viral infection causes extensive and persistent inflammatory changes along the neural pathways from

the spinal cord to the terminal ramifications in the skin. We believe that these changes are the probable source of the pain impulses and that, when the central nervous system is bombarded by too many pain stimuli for too long a time, a central pain mechanism is established with self-perpetuating circuits and aggravated by many and various stimuli.

We believe that medical attention should be focused on the preventive aspect of postherpetic neuralgia by perfecting the measures to reduce the severity of the acute attack (for example, therapy with chlortetracycline [Aureomycin], chloramphenicol [Chloromycetin], and posterior pituitary injection [Pituitrin]) and to provide adequate relief of pain during this acute stage. It should be stressed that many of the procedures that fail significantly to relieve postherpetic pain are quite effective in treating the discomfort of acute herpes zoster.

Once postherpetic neuralgia has become established, the vicious pain cycle sometimes can be broken and the process prevented from spreading and acquiring momentum. The simpler procedures are often more effective than the major ones, and analgesic blocking is the most effective nonsurgical method. The earlier treatment is started, the greater the chances of obtaining relief. Unfortunately, when the neuralgia has been present without abatement for several years, patients are rarely cured. Preoperatively, the patient must not be led to expect a cure but to regard the proposed procedure as effective if it can ameliorate the unbearable pain to the point where he can tolerate the residual discomfort. One can often succeed in stopping the sharp flashes of pain and reducing the degree of discomfort, although usually the involved skin is hypersensitive and retains a dull ache and deep soreness. Certain surgical procedures have been found to be effective, and our own policy has been to select one with a low morbidity, proceeding to the next only if a failure is encountered.

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TREATMENT OF ENTEROBIASIS AND ASCARIASIS WITH PIPERAZINE

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• Pinworm infestation in 60 patients was treated with piperazine citrate by mouth in a seven-day course. No advantages were seen in prolonging the treatment to 10 or 14 days, in dividing the daily dose, or in substituting piperazine phosphate or calcium dipiperazine dicitrate.

Ascariasis in 46 patients was treated with a single dose of piperazine citrate, and 34 were cured by this one-day treatment. A two-day treatment cured 50 out of 53 patients. The timing of the dose, whether before or after breakfast, had no discernible influence on the result.

Side-reactions in the form of urticaria, nausea, or diarrhea were seen but rarely in 400 patients who received the recommended dosage of 50 to 75 mg. of piperazine (calculated as the hexahydrate) per kilogram of body weight per day.

Recent studies have demonstrated the great effectiveness of relatively simple piperazine compounds against enterobiasis (pinworm infection) and ascariasis, opening a new approach to the chemotherapy of helminthiasis not only of man but of domestic animals as well.

Piperazine in Therapy of Enterobiasis

Because the adult female pinworm Enterobius vermicularis is frequently seen in stools or found in the perianal region by the patient or his parent, this parasite is the one most commonly implicated in diagnosis in the United States. It is estimated that approximately 16 million persons in the U. S. are infected, and, unlike many intestinal helminths, pinworm is not limited to the rural and the poor but is found in all urban economic classes. No other helminth parasite of man has such an extensive geographical distribution; surveys indicate that over 200 million persons in the world harbor it.

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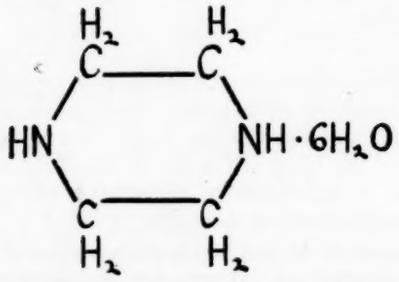
The piperazine citrate used in this study was supplied by Burroughs Wellcome & Company, Inc., Tuckahoe, N. Y., as Antepar; Sharp & Dohme, Philadelphia; and Winthrop-Stearns, Inc., New York. The piperazine phosphate was supplied by Thos. Leeming & Co., Inc., New York, in "chewable spheres" and wafer form.

A large number of drugs have been employed in the treatment of enterobiasis with varying degrees of success; the reported efficacy of a number of them is as follows: methylrosaniline chloride (gentian violet) 60-91%, oxytetracycline (Terramycin) 85-90%, piperazine cit-

rate 54-97%, phthalylsulfathiazole (sulfathalidine, Cremothalidine) 44-89%, tetrachlorethylene 47-55%, phenothiazine 60-82%, benzylphenylcarbamate (Diphenan, Butolan) 10-44%, thymyl *N*-isoamylcarbamate (Egressin) 30-52%, bacitracin 40%, and bacitracin and succinylsulfathiazole (Sulfasuxidine) 82%. Several of these agents are either too toxic, relatively therapeutically ineffective, require unrealistic quantities for successful therapy, or are too expensive; therefore, until recently, methylrosaniline has remained the drug of choice, with oxytetracycline in a secondary position.

Methylrosaniline, in enteric-coated tablets, is an effective, inexpensive therapeutic agent for the treatment of enterobiasis. It is not well tolerated by some individuals, and nausea, vomiting, diarrhea, abdominal pain, and lassitude occasionally follow the administration of repeated orally given doses, but these reactions quickly subside when the dosage of the drug is decreased or its administration is discontinued. Oxytetracycline is effective but expensive, especially when the treatment of a whole family is necessary. It is useful, however, in patients who do not tolerate methylrosaniline.

The effectiveness of piperazine against human enterobiasis has been shown by the clinical studies of Mouriquand, Roman, and Coisnard [1] and others.[2] Our studies on a large series of piperazine compounds indicate that most are effective against the mouse pinworm Syphacia and that their activity is related to their piperazine content. Piperazine citrate as a flavored syrup was used in most of the clinical studies, and each cubic centimeter of the commercially available syrup contains the equivalent of 100 mg. of piperazine hexahydrate, which is the form it assumes in aqueous solution. Tablets of piperazine citrate containing the equivalent of 500 mg. of piperazine hexahydrate are also available. The structural formula of piperazine hexahydrate is shown below:



The dosage employed has varied somewhat, but most workers employed the schedule shown in table 1, which is effective and safe. The early studies employed a dosage schedule of seven days' therapy and seven days' rest, followed by an additional seven days' therapy, a therapeutic regimen very similar to that used with methylrosaniline in the treatment of pinworm. The total daily dose of piperazine is divided into two or three portions and given at mealtime. Although the criteria of cure employed by several investigators have varied, in general, seven days after the completion of treatment a cellophane tape swab preparation was secured from the patient and this procedure continued for seven consecutive days. Any swab showing one or more eggs indicated a failure to cure, while failure to find eggs on all seven swabs was considered a cure. In general, this 14-day divided course of therapy was very effective (table 2), and from 85 to 97% cure rates were achieved. Differences in the cure rates can be explained by variations in dosages due to the broad weight categories, by what the patient interpreted as a teaspoonful of the piperazine syrup, and by post-treatment follow-up criteria of cure. White and Standen [2a] gave daily doses ranging from 50 to 108 mg. per kilogram of body weight, which probably explains their high cure rate of 97%. Bumbalo and others [2b] gave smaller amounts divided into three daily doses, which, in view of the success of a large single daily dose, may decrease the efficacy of the drug. Their cure rate was 85%. Rachelson and Ferguson [2d] obtained a cure rate of 89% in 150 patients infected with Enterobius.

TABLE 1.—*Total Daily Dose of Piperazine Used in Therapy of Enterobiasis*

Weight of Child, Lb.	Piperazine Citrate Syrup	Equivalent Piperazine Hexahydrate, Mg.
Up to 15	½ teaspoon daily	250
From 16-30	½ teaspoon b.i.d.	500
From 31-60	1 teaspoon b.i.d.	1,000
Over 60	2 teaspoons b.i.d.	2,000

Clinical observations in man suggest that adult pinworms are especially susceptible to piperazine, and our studies on the mouse pinworm Syphacia demonstrate conclusively the great efficacy of piperazine hydrochloride against adult worms and its relatively slight effect on those in the immature stages. These observations suggested that an interrupted treatment spread over several weeks might be especially effective, as it would allow time for immature forms to develop to the mature, susceptible stages. For the above reasons, in our early therapeutic trials of piperazine against Enterobius infections, we employed the split 14-day course of treatment and achieved a 92% cure rate in a group of patients [2c] (table 2). We found pinworm eggs in the perianal area of a number of these patients during the seven-day rest period between the two courses of therapy. Spread of infection in the family and self-infection were therefore both possible. Furthermore, it was felt that a shorter therapeutic regimen, if equally effective, would be advantageous. We therefore treated a number of patients infected with pinworms for 10 and 14 consecutive days with excellent results, obtaining cure rates of 89 and 97% respectively.

TABLE 2.—*Effect of Piperazine Citrate Syrup on Enterobius Vermicularis Infections in Man*

Observer	Dosage Schedule	Patients Treated, No.	Patients Cured	
			No.	%
	Two 7-day courses 1 wk. apart			
Brown and Chan [2c]	b.i.d.	24	22	92
White and Standen [2a]	b.i.d.	31	30	97
Rachelson and Ferguson [2d]	b.i.d.	150	134	89
Bumbalo and others [2b]	t.i.d.	47	40	85
Brown and Chan [2c]	14-day course, b.i.d.	39	38	97
Brown and Chan [2c]	10-day course, b.i.d.	57	51	89
Howie [15]	10-day course, b.i.d. and t.i.d.	58	49	84
Present study	7-day course, single dose	60	58	97

Inasmuch as two or three daily doses of piperazine given at mealtime may increase its absorption, thereby decreasing the concentration on the pinworms, we gave one group of patients the total daily dose one-half to one hour before breakfast followed by a glass of water. We thereby expected to greatly increase the concentration of the drug in the cecum and colon, the habitat of the pinworm. Chemotherapy was continued for only seven

TABLE 3.—*Results of Seven-Day Course of Piperazine Citrate Against Enterobius Infections* *

Patients Treated		Daily Dose as Piperazine Hexahydrate, Gm.	Therapeutic Results	
Weight, Lb.	No.		Cure †	Failure
41-50	1	1	1	..
51-60	7	1	7	..
61-70	6	2	6	..
71-80	8	2	8	..
81-90	11	2	10	1
91-100	9	2	9	..
101-110	7	2	6	1
111-120	4	2	4	..
121-130	5	2	5	..
141-150	1	2	1	..
151-160	1	2	1	..
Total	60		58	2

* Syrup given at a single dose before breakfast.
† Over-all cure rate, 97%.

consecutive days in an attempt to develop a short and therefore cheaper treatment regimen. Fifty-eight of 60 patients (97%) were cured by this course of therapy (table 3). These results are slightly superior to those of the 10-day course of therapy and at least as good as 14 days of therapy in which the total daily amount of piperazine was divided into two or three doses and given at mealtime. It would appear therefore from our studies that the seven-day course, giving the drug at one dose before breakfast, is not only as effective as longer courses with divided doses but reduces by as much as 50% the amount of piperazine required.

Several salts of piperazine other than the citrate have been found effective against pinworm. We recently treated 74 patients with piperazine phosphate, using a seven-day dosage schedule similar to that employed with the citrate syrup. The cure rate in this group was 89%. Piperazine phosphate is relatively insoluble and has a very high LD_{50}. We also found calcium dipiperazine dicitrate effective, and we succeeded in curing 10 out of 12 patients with a 14-day divided course of therapy. Piperazine adipate has also been reported to be effective against Enterobius.

Piperazine in Therapy of Ascariasis

According to Stoll's 1947 summary, 3 million persons in the United States, especially inhabitants of the mountainous and hilly areas of the South, harbor the large roundworm Ascaris lumbricoides, and he estimates that over 600 million persons in the world are hosts to this parasite. Hexylresorcinol (crystoids anthelmintic) has been the drug of choice against ascariasis for the past 25 years, and, except for local irritation and superficial burns of the buccal mucosa when the pills are chewed, there are no contraindications to its use; a single adult dose of 1 gm. is very effective. Santonin and oil of chenopodium have been widely used in the treatment of ascariasis; the former is not very effective in safe doses, and the latter has caused a number of fatalities even in the accepted dosage.

Oliver-Gonzales, Santiago-Stevenson, and Hewitt [3] demonstrated that the complex substituted piperazine 1-diethyl-carbamyl-4-methylpiperazine hydrochloride (Hetrazan), is relatively effective against Ascaris. Etteldorf and Crawford,[4] Ghanem,[5] and others have confirmed and extended these findings, and there is general agreement that this form of piperazine, when given for from 3 to 15 days, is effective against Ascaris, although its activity is somewhat irregular when given for less than 7 days.

Fayard [6] was the first to report on the treatment of Ascaris infections with piperazine (diethylenediamine). The active constituent of his syrup was piperazine hexahydrate. Adults were given 1.5 gm. of piperazine (equivalent to 3.5 gm. of piperazine hexahydrate) in the evening and a similar amount the following morning. Fayard reports that approximately 2,000 French patients were treated by cooperating physicians, who reported 70 to 95% of their patients passed ascarides, beginning usually on the second day of treatment and continuing on the following day. As many as 170 ascarides were passed by individual patients, and most of the worms were alive, although dead worms were also noted. Unfortunately post-treatment stool examinations were not routinely done, nor were egg counts made, and it is impossible, therefore, to determine the exact cure rate or the over-all worm reduction in Fayard's extensive series.

Brown and Sterman,[7] using the same daily amounts of piperazine citrate employed in enterobiasis divided into a morning and evening dose, achieved the following cure rates in ascariasis: five days' therapy, 46 of 50 cured (92%); four days' therapy, 13 of 15 cured (87%); three days' therapy, 14 of 15 cured (93%); and two days' therapy, 11 of 13 cured (85%). Basnuevo and others [8] and Swartzwelder, Miller, and Sappenfield [9] likewise report excellent results with 3 to 15 days of piperazine therapy.

In view of the excellent results of the two-to-five-day course of therapy, and in an attempt to increase the therapeutic efficacy and shorten the course of treatment, we increased the total daily dose of piperazine and gave it as a single dose 1½ to 3 hours after breakfast on one day or two consecutive days (table 4). No special dietary regimen was suggested, there was no pretreatment fasting, and no purgatives were employed. A dilution egg count was made on the stool of each patient before treatment; two to three weeks after the completion of therapy two fecal smears from each patient were thoroughly examined, and if Ascaris eggs were present an egg count by the Stoll technique was made. Results of this therapy were found to be excellent: With one day's therapy, 34 out of 46 patients were cured (74%) and the total

TABLE 4.—*Dosage Schedule for One-and-Two-Day Treatment of Ascariasis with Piperazine*

Patient's Weight, Lb.	Daily Dose of Citrate Syrup, Cc.	Daily Dose as Hexahydrate, Gm.
30-50	20	2.0
51-100	30	3.0
101 and over	35	3.5

egg count was reduced by 92%. With two days' therapy, 50 out of 53 patients were cured (94%) and the total egg count was reduced by 99.6%. The 12 patients who were not completely cured by the one dose of piperazine received amounts ranging from 64 to 122 mg. per kilogram, with a mean of 82 mg. per kilogram. Swartzwelder, Miller, and Sappenfield [10] report that they cured 16 of 17 lightly infected patients with a single dose of piperazine ranging from 43 to 70 mg. per kilogram.

TABLE 5.—*Effect of Piperazine Citrate on Trichuris Trichiura Infections* *

Case No.	Age, Yr.	Weight, Lb.	Daily Dose as Piperazine Hexahydrate, Gm.	Treatment, Days	Trichuris Egg Count/Cc. of Feces	
					Before Treatment	After Treatment
9	6	50	1	5	3,000	1,000
16	8	60	1	5	3,700	400
13	7	56	1	5	1,700	1,300
28	10	76	2	5	1,400	1,600
12	7	49	1	5	2,200	2,100
24	8	65	2	5	3,800	3,300
32	16	160	2	5	1,600	2,000
39	11	58	1	5	2,700	500
21	8	54	1	5	700	100
35	14	110	2	5	200	200
Total	..	..	..	..	20,700	12,500
1A	4	18	0.4	7	109,500	113,000

* Piperazine citrate syrup was administered twice daily (in the morning and afternoon). Stoll egg counts were done before and 15 days post-treatment.

Fields, Selly, and Guicherit have confirmed our studies on the effect of one-day therapy. They report a cure rate of 51.7% in "heavily" infected patients and 86.2% in "lightly" infected patients, with an over-all cure rate of 69%. Hoekenga reports an 85% cure rate from a single dose of piperazine phosphate in wafer form. It would appear that the two-day course of therapy with the increased dosage is the treatment method of choice, as it completely cures approximately 20% more of the patients than does the single-day therapy. It is also as effective or slightly more effective than the five-day course of treatment in which the drug is given in smaller daily doses but a 30% greater total dose. The two-day course of therapy for ascariasis has a special advantage in clinic practice and mass-treatment programs. The first day's treatment can be administered by the physician, and an additional safe amount can be given to the patient to be taken at home on the following day.

To ascertain the effect of food on the efficacy of piperazine against Ascaris, 21 patients were given the one-dose therapy and the drug was administered before breakfast. The cure rate in this group was 71% and the total egg count reduction was 95%, which is probably not significantly different from the results achieved by a single dose given after breakfast. Apparently the presence of food in the digestive tract has little, if any, effect on the activity of piperazine against Ascaris.

The ascarides usually are passed by the patient on the first, second, or third day of treatment and are immobile and relaxed, though not dead, for when they are placed in warm saline solution they regain their activity. Our in vitro studies and those of others indicate that solutions of piperazine produce a state of narcosis and relaxation of the worms after a few hours. Presumably, the worms are passed out of the host because they can no longer maintain their position in the small intestine by pressure against its wall and their resistance to intestinal peristalsis.

Effect of Piperazine on Other Helminths

Trichuris Trichiura.—The effect of piperazine on Trichuris trichiura, the whipworm of man, is controversial. Dunn [11] reported an 18% cure rate among 22 children treated for three days with piperazine hexahydrate at the rate of 75 mg. per kilogram of body weight. Others [9] noted no significant reduction in egg counts of patients with light Trichuris infections when treated with a wide range of dosages of piperazine citrate. Our results in a group of patients treated for five or seven days with piperazine citrate confirm the findings that piperazine in the usual amount is relatively ineffective against Trichuris (table 5). It is possible that longer courses of therapy might be effective.

Piperazine adipate, according to Dunn,[11] is highly effective against Trichuris, and he reports a 90% cure rate among 31 children treated for three days. He gave 300 mg. per year of age to a maximum of 1,800 mg. daily. These results were so outstanding that we wished to confirm them and therefore treated three heavily infected children. The children were hospitalized in order to supervise the administration of the drug and to examine the stools for adult Trichuris during treatment. Although our patients weighed only 35 to 41 lb. (15.9 to 18.6 kg.) each was given piperazine adipate (equivalent to 1.75 gm. of piperazine hexahydrate) as a single dose before breakfast on three consecutive days. Only one adult Trichuris was found in the stools during treatment and 14 days post-treatment; egg counts failed to reveal a significant reduction (table 6).

Necator Americanus.—Swartzwelder and others [9] report an 83% reduction in the Nector americanus (hookworm) egg count of the patient they gave piperazine citrate for 10 days, and our own human and animal studies indicate it is of slight value against hookworm. In view of the excellent results achieved against hookworm by a single dose of tetrachlorethylene, piperazine would appear to have little to offer in the treatment of this infection.

TABLE 6.—*Effect of Piperazine Adipate on Trichuris Trichiura Infections*

Age, Yr.	Weight, Lb.	Daily Dose as Piperazine Hexahydrate, Gm.	Treatment, Days	Trichuris Egg Count/Cc. of Feces	
				Before Treatment	After Treatment
5	35	1.75	3	51,100	44,200
6	39	1.75	3	229,400	335,800
7	41	1.75	3	23,800	15,600

Strongyloides Stercoralis.—Jones treated three patients infected with Strongyloides with 3 gm. of piperazine citrate a day for 7 to 10 days. One patient received 6 gm. of the drug daily for an additional seven days. Larvae of Strongyloides were demonstrable in the stools of all three

patients after the completion of treatment, but whether the number of larvae present in the stools was reduced was not indicated.

Hymenolepis Nana.—Infections with Hymenolepis nana are not cured by 10 days of therapy with piperazine citrate in the usual dosage according to Swartzwelder and others.[9]

Trichinella Spiralis.—Adult Trichinella spiralis are eliminated from mice by large doses of piperazine, but its effect on human infection with the parasite is unknown. We also failed to cure two patients with heavy infections of Giardia lamblia with seven days of piperazine citrate therapy.

Toxicity

Clinical experience with piperazine dates back to the 1890's, when it was used extensively in gout, urinary lithiasis, and rheumatism on the mistaken theory that it increased the solubility of urates and increased uric acid excretion. Daily doses ranging from 0.5 to 10.0 gm. were employed. Patients were given 1 gm. daily for 30 to 150 days, 1 to 2 gm. daily for 60 days, 3 gm. daily for 15 days, and 6 gm. daily for 6 days. Many of the reports on the use of piperazine in man mention the absence of side-reactions. Hanzlik,[12] however, in an extensive article summarizing the use of piperazine, calls attention to undesirable side-reactions such as urticaria, headache, vomiting, diarrhea, tremor, incoordination, and muscular weakness. The side-reactions were observed most frequently after the administration of large doses in aged or debilitated patients.

The recent extensive use of piperazine citrate in the treatment of enterobiasis has given additional information on its toxicity. When used in recommended doses of 50 to 75 mg. per kilogram (piperazine hexahydrate) daily for adults for 14 days, very few side-reactions have been observed except for occasional urticaria. We have treated over 400 patients with doses usually not exceeding 75 mg. per kilogram per day, and only 3 patients experienced nausea and one diarrhea. White and Standen [13] report side-effects in 20 patients who were given piperazine hydrate for pinworm. Giddiness, lack of coordination, difficulty in focusing vision, and a sense of detachment were noted. These effects, for the most part, were mild, and recovery was rapid when therapy was stopped. These workers suggest that the side-effects were due to the drug being taken in doses considerably in excess of their recommended 50 to 75 mg. per kilogram. The overdosage, which was as great as 100%, was due presumably to the great variation in the capacity of the domestic tablespoon that was used in measuring the syrup and also to the high meniscus formed by the thick syrup embodying the piperazine, which also would lead to even greater amounts being taken.

Recently Sims [14] reported the following toxic effects in a patient who was treated for pinworm: sense of detachment, flashes on closing the eyes at night, and the dropping of articles. Sims was employing a dosage schedule of 75 mg. (piperazine hexahydrate) per kilogram of body weight. The patient weighed 130 lb. (59 kg.) and, hence, the calculated dose was 4.4 gm. daily; yet, due to the large size of the tablespoon with which she measured the syrup, this patient was evidently taking over 6 gm. per day. In the course of a week she took 42 gm. instead of the intended 31 gm.

Howie [15] treated 58 patients with rather large amounts of piperazine hexahydrate, giving 56 to 133 mg. per kilogram daily, with mean daily dose of 83 mg. for 10 days. Vomiting, vertigo, difficulty in reading, dropping of objects, or memory defects were noted by five patients beginning on the fifth to the seventh day of treatment. Three of these five patients were being retreated with larger than average doses of piperazine due to the failure of the initial 10 days of therapy. Rachelson and Ferguson [2d] noted one or more of the following side-effects from piperazine therapy in 7 of their 150 patients: nausea, urticaria, erythema multiforme, mild diarrhea, slight nausea, and lethargy. Complete blood cell counts and urine examinations performed in 25 of their patients, including those with urticaria and erythema multiforme, revealed no abnormalities. There were no ill-effects in the two pregnant women treated; one of them delivered a normal infant one week after the completion of therapy.

We recently observed nausea; vomiting; coarse tremor of hand, arm, and leg muscles; and vertigo in a patient who had completed five days of piperazine citrate therapy for pinworm. The patient also complained of a sense of detachment and difficulty in vision. He received 30 mg. per kilogram of the drug per day, which is in the lower dosage limits. He was, however, suffering from hypertension and chronic nephritis and presumably could not excrete the absorbed piperazine at the normal rate. Accurate data on the absorption, excretion, and concentration of piperazine in the blood are not available due to the difficulties in quantitating it in biological fluids. There is evidence that as much as 20% of the piperazine given by mouth is excreted in the urine, and presumably a considerably larger percentage is absorbed through the intestine. Studies of chronic piperazine intoxication by de Beer failed to reveal a significant effect on the red blood cell or white blood cell counts. The LD_{50} (oral) dose of piperazine citrate for mice is 11 gm. per kilogram and of piperazine phosphate 20 gm. per kilogram.

Conclusions

Piperazine citrate is a most effective drug for the treatment of enterobiasis; a single course of therapy will cure as high as 97% of the infections. A seven-day course of therapy, giving the piperazine before breakfast, is as effective as longer courses in which the drug is given two or three times daily at mealtime. A two-day course of therapy, with a higher dosage schedule than that employed in enterobiasis, will cure approximately 94% of Ascaris infections.

Piperazine citrate, when employed in the recommended amounts, is well tolerated by the great majority of patients. Mild nausea, vomiting, and urticaria may occur rarely. Overdosage may cause neurological side-effects, and patients with nephritis may experience similar side-effects from standard doses of piperazine.

The following parasitic infections do not respond or respond minimally to piperazine therapy; Necator americanus (hookworm), Trichuris trichiura (whipworm), Strongyloides stercoralis, Hymenolepis nana (dwarf

tapeworm), and Giardia lamblia. Adult Trichinella spiralis organisms are removed from mice by piperazine therapy.

600 W. 168th St. (32) (Dr. Brown).

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The Acute Abdomen.—It is better to have a definite policy of management in the doubtful case rather than to be panicked into an immediate and possibly unnecessary operation. The following measures are beneficial to the patient in either situation until the diagnosis is clarified and the indications for or against operation can be formulated. Hospitalize the patient. Establish a baseline on the pulse, blood pressure and temperature, and maintain a close chart on these signs. Similarly obtain an initial leukocyte and red blood count and repeat at four to six hour intervals. Measure the intake and output of fluids. In the acutely ill, elderly patient an indwelling bladder catheter provides insurance for an accurate record of urinary output. Intravenous fluids to correct an existing dehydration and maintain fluid and electrolyte balance should be administered. Insert a Levin tube into the stomach and connect to a continuous suction apparatus if there is repeated vomiting or distention. Record the dosage and frequency of narcotic administered. Determine the blood amylase level. Obtain flat and upright roentgenograms of the abdomen and a chest x-ray. Type and cross-match the patient's blood.

Reappraisal of the patient at intervals of no more than four hours is essential until the decision is clear. Routine use of antibiotics is unwise since the developing clinical picture will be distorted, and an erroneous decision made against surgical intervention in a situation best managed by early operation. . . . On such a program the patient's welfare will be best protected except in cases of free perforations or massive hemorrhage, and the diagnosis of these emergencies should quickly be evident from the clinical picture as well as the investigative measures outlined.—E. T. Boles Jr., M.D., R. M. Zollinger, M.D., The Acute Abdomen—Medical Aspects, *The Medical Clinics of North America*, March, 1955.

CLINICAL NOTES

NEPHROTIC SYNDROME IN CONGENITAL QUARTAN MALARIA

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The patient whose case is to be reported had manifestations of the nephrotic syndrome as a result of infection with Plasmodium malariae. The evidence indicated that the child acquired malaria congenitally from the mother, a narcotic addict, who had acquired her infection by syringe inoculation. The patient's clinical course, the changes in concentration of the plasma proteins and lipids, and the quantitative urinary output of protein and formed elements were studied during therapy with chloroquine phosphate. A complete remission of the nephrotic syndrome occurred.

Report of a Case

The patient, a 21-month-old Negro female, was admitted to the Clinical Center of the National Institutes of Health with a history of facial and abdominal swelling of three months' duration. She was delivered out of wedlock in the prison section of District of Columbia General Hospital, Washington, D. C. The delivery was normal and the neonatal course uneventful. The baby was nursed by the mother for the first six weeks and thereafter was cared for by foster parents. She remained in Washington, D. C., or its environs, until admission to the Clinical Center. Her development was normal; she smiled in the first few months, sat unsupported at 6 months, and stood alone and was on a regular diet before one year. She received no blood transfusions.

The father of the patient is unknown. The 26-year-old Negro mother, a native of Washington, D. C., had never left the Washington area. For several months before delivery she frequently took heroin injections with nonsterilized syringes used by other addicts. She had attacks of chills, sweats, and fever about every other day during the two to three-week period immediately after delivery. Shortly after the patient's delivery the mother was sent to the U. S. Public Health Service Hospital, Lexington, Ky., where she was treated for heroin addiction. When it was learned that the daughter had malaria, a thick blood preparation of the mother's blood was examined; P. malariae was found (fig. 1). A course of therapy with chloroquine phosphate and primaquine phosphate was instituted. No plasmodia have been seen after therapy.

Present Illness.—When the patient was 15 months of age she was admitted to a Washington, D. C., hospital with a 10-day history of high fever recurring almost every afternoon. Penicillin therapy had no effect. No gastrointestinal or respiratory symptoms were present. The temperature was 101.4 F (38.8 C) and the pulse rate 120 per minute. The pharynx was injected, and the spleen was palpable 3 cm. below the costal margin. The remainder of the physical examination was normal. Urine samples contained from 70 to 1,000 mg. of protein per 100 ml. in casual specimens. Up to 10 red blood cells and 50 epithelial cells and white blood cells per high-power field were present in the urine sediment, but no casts were noted. Blood examination showed 10 gm. of hemoglobin per 100 ml., 6,700 white blood cells per cubic millimeter, 34% polymorphonuclear leukocytes, 66%

From the National Heart Institute.

lymphocytes, and a few polychromic red blood cells. A bisulfite test for sickling was negative. Subsequent blood studies showed a fall in the blood hemoglobin to 8 gm. per 100 ml., and white blood cell counts ranged between 5,500 and 11,100 per cubic millimeter. The blood urea nitrogen level was 9 mg. per 100 ml. A throat culture showed diplococci. The agglutinations for enteric organisms and the heterophil antigen test were negative. X-rays of the lungs and heart were normal. An intravenous

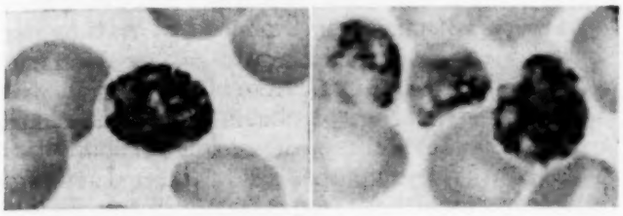

Fig. 1.—Blood smear of mother before therapy with chloroquine phosphate, showing Plasmodium malariae.

pyelogram showed normal kidney, ureteral, and bladder outlines. The temperature dropped from a peak of 104 F (40 C) on the day of admission to normal by the second day. On the seventh day another spike to 104 F occurred. The temperature fell to normal the next day without antipyretic or antibiotic therapy. Except for the enlarged spleen, a few scattered lymph nodes, equivocal hepatomegaly, and an injected pharynx, the physical examination remained normal. "Strange cells" were observed in the blood smear on the second hospital day. These cells were not identified, and it was not suspected that malaria parasites were present. The patient was discharged on the eighth day with a diagnosis of pyelonephritis and a blood dyscrasia of unknown type.

After discharge, irregular bouts of fever continued from one to three times per week. They occurred most commonly at night and were frequently associated with bizarre extraocular movements and unresponsiveness. No chills or sweats were noted, but the patient's skin often felt icy cold. When the patient was 19 months of age, abdominal swelling was noted, and at 20 months she developed leg and facial edema. She was seen briefly at a Baltimore hospital where, on the basis of the 4+ proteinuria, edema, and an enlarged spleen, a diagnosis of the nephrotic syndrome, and possibly sickle cell anemia, was made. She was referred to the National Institutes of Health for study.

On admission to the Clinical Center the patient was edematous and appeared chronically ill. The temperature was 98.6 F (37 C), pulse was 142 per minute, blood pressure 97/68 mm. Hg, respiratory rate 38 per minute, weight 24 lb. (10.9 kg.), head 46 cm., chest 49 cm., abdomen 51 cm., and crown-to-heel length 86 cm. There was a small amount of serous exudate in each nostril, and a few isolated anterior and posterior cervical lymph glands, 0.25 cm. in area, were felt. A firm, regular, nontender spleen was palpable 5 cm. below the costal margin, and the liver edge was palpable 1 cm. below the costal margin. An abdominal fluid wave and shifting dulness were elicited. Pretibial and facial edema were present. A capillary fragility test was positive.

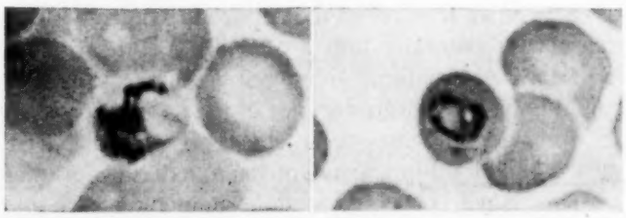

Fig. 2.—Blood smear of child before therapy with chloroquine phosphate, showing Plasmodium malariae.

Laboratory Data.—On admission, a thick blood smear revealed the presence of P. malariae in large numbers (fig. 2). The blood hemoglobin level was 11.8 gm. per 100 ml., and the reticulocyte count 1.9%. There were 12,700 white blood cells per cubic millimeter, with 45% polymorphonuclear leukocytes, 43% lymphocytes, 8% monocytes, and 4% eosinophils. The urine contained 4+ protein and a moderate number of red blood cells, epithelial cells, oval fat bodies, and fatty casts. The specific gravity was 1.027. The following plasma values were obtained: total cholesterol 288 mg. per 100 ml., carbon dioxide content 25 mEq. per liter, chloride 109 mEq. per liter, sodium 136 mEq. per liter, potassium 4.9 mEq. per liter, calcium 10.1 mg. per 100 ml., phosphorus 4.9 mg. per 100 ml., creatinine 0.5 mg. per 100 ml., uric acid 4 mg. per 100 ml., bilirubin 0.4 mg. per 100 ml., and plasma hemoglobin 4.4 mg. per 100 ml. The endogenous creatinine clearance was 136 ml. per minute per 1.76 sq. m. The cephalin flocculation test was negative. A stool culture for pathogens was negative, and no ova or parasites were seen. The Kolmer complement-fixation and Venereal Disease Research Laboratory flocculation tests were negative. Electrocardiograms showed sinus tachycardia. X-ray studies revealed normal bone age, normal cardiac silhouette, and normal lung markings.

Course.—The patient was given 0.125 gm. of chloroquine phosphate on admission, 0.063 gm. every six hours for four doses, and then 0.063 gm. once a day for a week. Penicillin and oxytetracycline (Terramycin) were given for two days because of loose stools. She was offered a diet containing 200 mg. of sodium. The temperature rose to 103.6 F (39.8 C) 12 hours after admission and to 100.4 F (28.0 C) the day after admission but otherwise remained normal. The spleen was not palpable after the third day. A capillary fragility test was normal on the

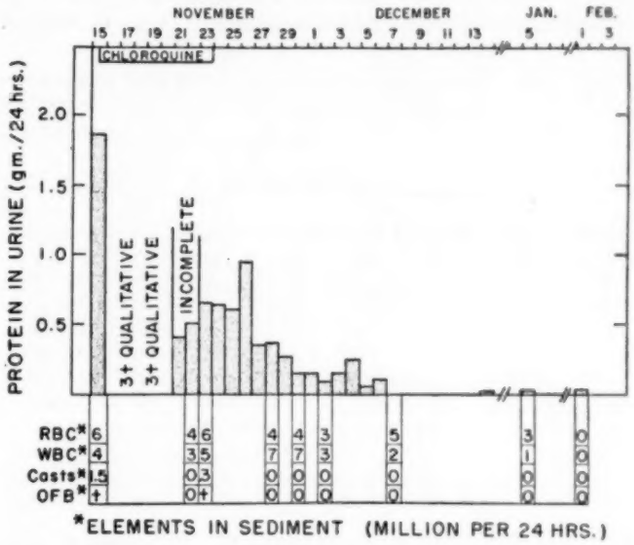
NOVEMBER
DECEMBER
JAN.
FEB.
15 17 19 21 23 25 27 29 1 3 5 7 9 11 13 5 1 3
CHLOROQUINE
PROTEIN IN URINE (gm./24 hrs.)
2.0
1.5
1.0
0.5
3+ QUALITATIVE
3+ QUALITATIVE
INCOMPLETE
RBC* 6 4 6 4 4 3 5 3 0
WBC* 4 3 5 1 1 3 2 1 0
Casts* 1.5 0.3 0+ 0 0 0 0 0 0
OFB* + 0+ 0 0 0 0 0 0 0
*ELEMENTS IN SEDIMENT (MILLION PER 24 HRS.)

Fig. 3.—Summary of observations on urine. RBC, red blood cells; WBC, white blood cells and renal epithelial cells; OFB, oval fat bodies. Casts were predominately granular and hyaline.

fifth day. A 9% fall in body weight occurred during the first 10 days. Her appetite increased markedly after the sixth hospital day and remained good until discharge. No facial or pretibial edema was detectable after the 10th hospital day. A few parasites were observed in a smear made eight hours after beginning therapy, but thick smears on numerous subsequent occasions for six months after treatment were negative. Addis count and results of quantitative urine protein determinations appear in figure 3. A progressive decrease to normal in daily urine output of protein, casts, and cellular elements was observed.

Plasma Protein and Lipid Studies.—Samples of plasma were analyzed in the Aminco model B electrophoresis apparatus, with a sodium diethyl barbiturate buffer of pH 8.6 to 8.7 and ionic strength 0.1. The early lipemic samples were clarified as necessary by high-speed centrifugation. Total protein for each sample was determined refractometrically, with results expressed as grams per cent dry weight of plasma protein (including protein-bound lipid and carbohydrate). The results appear in table 1. The presence of a chronic malarial infection, which will often give rise to hypergammaglobulinemia, may have prevented the development of the hypogammaglobulinemia usually observed in the nephrotic syndrome.[1] A progressive increase in the albumin and a decrease in the alpha and beta globulin concentrations to normal occurred after chloroquine phosphate therapy.

The composition and distribution of the serum lipoproteins shown in table 2 were determined by chemical analysis of ultracentrifugally separated fractions.[2] In the pretreatment sample, both the lowest density (<1.019) and the intermediate density (1.019-1.063) fractions were increased, the former strikingly so. The high density (>1.063) lipoproteins were markedly reduced.

TABLE 1.—*Course of Plasma Protein Concentrations in Patient with Quartan Malaria*

Date	Total Protein, Gm./100 Ml.	Albumin, Gm./100 Ml.	Alpha Globulin, Gm./100 Ml.	Beta Globulin, Gm./100 Ml.	Gamma Globulin, Gm./100 Ml.
11/16	6.6	0.77	1.6	3.2	0.99
11/17	Chloroquine phosphate therapy started				
11/29	7.2	2.39	2.9	1.2	0.77
12/15	7.9	3.77	1.5	1.8	0.76
1/ 4	7.1	3.85	1.3	1.3	0.74
2/ 2	7.5	4.1	1.5	0.95	0.95
Normal adult range	7.2-8.8	4.0-5.0	0.8-1.5	0.9-1.3	0.6-1.6

The cholesterol–phospholipid ratio in the intermediate density fractions was less than unity. With a few exceptions this last finding has been observed only in liver disease associated with biliary obstruction and jaundice. Correspondingly, the serum cholesterol–phospholipid ratio was reduced and the free cholesterol–total cholesterol ratio was increased, as is commonly seen in liver disease. However, the triglycerides were markedly increased and the serum was turbid; these findings are characteristic of the nephrotic syndrome.[2] After chloroquine phosphate therapy the abnormal findings characteristic of liver disease were the first to return to normal. The lipoprotein picture two weeks after therapy was characteristic of mild nephrotic syndrome as observed in our laboratory. The subsequent patterns showed progressive improvement, with a normal pattern appearing six weeks after therapy.

TABLE 2.—*Results of Plasma Lipoprotein Fractionations in Patient with Quartan Malaria*

	Plasma						Densities of Various Ultracentrifugal Fractions										
							1.019				1.019-1.063				1.063		
	Mg./100 Ml.				TC	FC	Mg./100 Ml.			TC	Mg./100 Ml.			TC	Mg./100 Ml.		TC
Date	TC *	FC	Pl	Tg	Pl	TC	TC	Pl	Protein	Pl	TC	Pl	Protein	Pl	TC	Pl	Pl
11/16	288	167	509	825	0.57	0.58	107	169	70	0.63	150	241	177	0.62	21	79	0.27
11/17	Chloroquine phosphate therapy started						...	...	..	....	...	...	...	....	..	..	....
12/ 1	364	88	400	316	0.91	0.24	48	72	30	0.67	243	169	145	1.44	60	135	0.44
12/15	235	50	278	151	0.85	0.21	28	41	..	0.68	145	107	97	1.36	49	134	0.37
1/14	138	37	179	179	0.77	0.27	10	25	16	0.40	93	74	56	1.26	36	84	0.43
2/ 2	174	42	214	160	0.81	0.24	26	38	16	0.68	98	74	56	1.32	36	97	0.37
Mean value in young adults	179	48	226	...	0.79	0.27	23	28	17	0.82	103	74	60	1.39	49	123	0.40

* TC = total cholesterol, FC = free cholesterol, Pl = phospholipids, Tg = triglycerides.

Comment

Both the mother and the patient apparently contracted malaria by means other than mosquito transmission. This assumption is based on the rarity with which mosquito-induced quartan malaria occurs in the United States. The patient responded promptly to a brief course of therapy with chloroquine phosphate and has had no recurrence of symptoms or parasitemia for over one year. In view of the history of narcotic addiction in the mother, involving intravenous injections with nonsterile equipment used by other addicts, it seems likely that she contracted malaria by inoculation. Falciparum malaria is commonly transmitted by this method, but there have been only rare instances of an occurrence of P. malariae in drug addicts resulting from use of contaminated syringes.[3] On the other hand, P. malariae infections have not uncommonly been transmitted by transfusions of large quantities of blood.[4]

In the child, with no history of injections of blood, congenital transmission seems the most likely explanation of the infection, since the mother probably contracted malaria shortly before delivery and was observed to have parasitemia when examined 21 months later. Since tissue forms of malaria parasites are thought not to occur in malaria resulting from blood inoculation, the mode of transfer of the plasmodia to the child remains for consideration. While the most likely possibility seems to be the transplacental passage of infected red blood cells, it is conceivable that parasites might have been transferred without passage of intact red blood cells. Malaria has been transmitted to man, as well as to monkeys and birds, by the oral administration of infected blood.[5] Passage of infected red blood cells or of free parasites into the amniotic fluid or possibly into the milk, with subsequent ingestion, is also to be considered. While circumstances seldom allow proof that a case of malaria in an endemic area is congenital, there have been instances in which blood from newborn and less than 7-day-old infants was found to contain malarial parasites (P. vivax, P. falciparum, and, less commonly, P. malariae), thus establishing beyond doubt that congenital malaria does occur.[6]

It is highly probable that the association of the nephrotic syndrome with quartan malaria is more than a coincidence, since many reports describe the occurrence of some or all features of the nephrotic syndrome in patients with naturally and artificially acquired quartan malaria.[7] Antimalarial treatment in these patients resulted in prompt disappearance of the nephrotic picture. In observing the long-term effects of mosquito-transmitted and blood-inoculated quartan malaria in 38 adult humans, Boyd [8] observed proteinuria in all: a trace in 24 patients and from 2+ to 4+ in 14. Edema limited to the lower extremities occurred in four instances, and edema plus ascites or facial edema occurred in two others. According to current concepts, autoantibodies may be involved in the pathogenesis of glomerular nephritis and the nephrotic syndrome. The finding of complement-fixing antibodies to antigen derived from human red blood cell stroma [9] and the frequent occurrence of

false-positive serologic tests for syphilis in malaria, indicate that antibodies against human tissue antigens may occur in malaria. The possibility that the malaria parasite may serve as the stimulus for the production of antibodies capable of attacking the kidney should be considered. Paradoxically, it is of interest to note that the induction of malaria due to P. vivax has been reported to result in remission of the nephrotic syndrome.[10]

Summary

In a case of the nephrotic syndome due to congenital infection with Plasmodium malariae in a 21-month-old child, the malaria was probably established in the mother, a narcotic addict, by the use of unsterilized needles and syringes used in common with other addicts. Serial quantitative studies of plasma proteins and lipoproteins and of urinary protein and formed elements were made in the child during chloroquine phosphate therapy, which resulted in elimination of the parasitemia and remission of all symptoms and signs of malaria and the nephrotic syndrome.

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ACUTE ADRENAL CORTICAL INSUFFICIENCY

PRECIPITATION BY INFECTION DURING PROLONGED CORTISONE TREATMENT

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and
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There is considerable evidence that cortisone from either exogenous or endogenous sources can cause a suppression of the function of the adrenal cortex. In 1935 Kepler noted that patients with a hyperfunctioning adrenal cortical tumor would have atrophy of the contralateral adrenal cortex and that these patients on occasion would die in a state of shock and collapse.[1] Ingle produced atrophy of the adrenal cortex in rats by administration of large amounts of cortin.[2] It has been demonstrated in humans that histopathological alterations occur in the adrenal cortex after the administration of cortisone. These changes include reduction in the total weight of the gland, narrowing and pallor of the cortex, and loss of lipid.[3] The depression of adrenal cortical function by cortisone has been further demonstrated by observing that cortisone-treated patients fail to respond in the usual manner to test doses of corticotropin. It has been shown by McIntosh and Holmes that the response of the circulating eosinophils and urinary 17-ketosteroid excretion is very similar to that of a group of patients with known adrenal cortical hypofunction (Addison's disease).[4] Recently, there have been a number of reports indicating that the added stress of surgery may precipitate severe adrenal cortical insufficiency in persons whose pituitary-adrenal axis has been rendered inoperative by the prolonged use of cortisone.[5] The stress of severe vomiting and diarrhea appeared to be the precipitating factor in causing acute adrenal cortical insufficiency reported by Keitzer and Cheek in a patient on long-term adrenal steroid treatment.[6]

Review of the literature to date fails to reveal any specific instance in which infection precipitated serious adrenal cortical insufficiency in patients on prolonged adrenal steroid therapy, although this possibility has been suggested.[7] The present report concerns an adult female who had received cortisone for a prolonged period and in whom acute adrenal cortical insufficiency was precipitated by pneumonia.

Report of a Case

A 34-year-old female was admitted to the hospital on March 13, 1955, with complaints of shortness of breath and pain in the right side of the chest that had been present for approximately 12 hours. She had developed rheumatoid arthritis 10 years previously and in April of 1951 had been started on therapy with cortisone given orally. The dose of cortisone had varied from 25 to 75 mg. daily according to her symptoms. For several months prior to admission the dose had been 50 mg. daily. She had never manifested any obvious evidence of the usual undesirable physiological side-effects.

At the time of admission the patient appeared acutely but not seriously ill. Temperature was 100 F (37.8 C), pulse 88 per minute, respiration 20 per minute, blood pressure 70/40 mm. Hg. She was dyspneic, and moist rales were heard over the entire right lung field. The evidence of chronic rheumatoid arthritis was noted. Leukocyte count at the time of admission was 21,000 per cubic millimeter; hemoglobin level, 13.7 gm. per 100 cc.; and hematocrit 44%. A throat culture showed normal flora. A single blood culture was sterile. Sputum cultures were not obtained due to a clerical error. Chest x-ray showed an infiltrative process involving the right midlung field, which was interpreted as bronchopneumonia.

The patient was given 300,000 units of procaine penicillin intramuscularly, and cortisone was ordered in dosages of 25 mg. three times daily. During the afternoon of the first hospital day the patient began to cough up bloody sputum. Because of right pleuritic chest pain she received 50 mg. of meperidine hydrochloride on two occasions. She was seen by a physician at 11 p. m., at which time she appeared comfortable. Temperature was 99 F (37.2 C), pulse rate, 84 per minute, respiration 22 per minute.

At 1 a. m. of the second hospital day, the patient was noted by the nurse to be in acute distress. Her blood pressure was 88/44 mm. Hg and her pulse rate, 140 per minute. Shortly afterward she was first seen by one of us (R. L. C.). She appeared acutely and critically ill. The blood pressure and peripheral pulsations were not obtainable. Heart rate was 150 per minute with regular rhythm. The heart sounds were very distant. One thousand cubic centimeters of sodium chloride solution containing 4 mg. of levarterenol bitartrate was started immediately intravenously. Sixty cubic centimeters of aqueous adrenal extract was given intravenously and the patient placed in an oxygen

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tent. Within 10 minutes the blood pressure was obtainable at 40/0 mm. Hg. One hundred milligrams of hydrocortisone and one million units of penicillin were added to the intravenous infusion. By adjusting the flow, the systolic blood pressure was maintained above 100 mm. Hg. Three hundred milligrams of cortisone was given intramuscularly and a polyethylene catheter was inserted into a vein to facilitate giving intravenous fluids. An electrocardiogram showed tachycardia (with rate of 120 per minute) with nonspecific T-wave changes.

The patient's condition remained precarious throughout the second hospital day. The temperature varied from 98.4 to 99.2 F (36.8 to 37.3 C). It was necessary to continue an infusion of levarterenol bitartrate intravenously to maintain the blood pressure above shock levels. On this day the patient received 2,000 cc. of sodium chloride solution and 4,000 cc. of 5% glucose solution intravenously, containing a total of 300 mg. of hydrocortisone and 48 mg. of levarterenol bitartrate. Desoxycorticosterone acetate, 30 mg. in divided doses, was given intramuscularly. In addition she received 4 gm. of potassium chloride orally and 500 cc. of whole blood intravenously.

During the third hospital day it was still necessary to maintain the blood pressure level with intravenously given levarterenol bitartrate. Her condition remained very poor; she was semiresponsive and on occasions uncooperative. Examination revealed a pleural friction rub and many fine rales over the right lung field anteriorly and laterally. The heart rate was 120 per minute with a regular rhythm. On this day the patient received 1,000 cc. of sodium chloride solution and 1,500 cc. of 5% glucose solution, containing a total of 50 mg. of levarterenol bitartrate and 250 mg. of hydrocortisone. Therapy with penicillin in large doses was continued. Therapy with streptomycin, 0.5 gm. intramuscularly twice daily, and cortisone, 75 mg. intramuscularly every eight hours, was begun. Any attempt to discontinue the infusion of levarterenol bitartrate resulted in a precipitous drop of the blood pressure level. In the evening the patient exhibited signs of fluid retention, including puffiness of the face, minimal distention of the neck veins, and a moderately tender liver edge 5 cm. below the right costal margin. No peripheral edema was demonstrated. Because of fluid retention and rapid heart rate, digitalization was accomplished rapidly with intravenously given lanatoside C. The pulse rate slowed to 84 per minute and a diuresis of 2,300 cc. occurred during the next 12 hours.

On the morning of the fourth hospital day, the patient was alert and complained of being hungry. At this time serum sodium level was 131 mEq. per liter; chloride, 106 mEq. per liter; potassium, 5.2 mEq. per liter; carbon dioxide, 20 mEq. per liter; and nonprotein nitrogen, 39 mg. per 100 cc. Digitalization was maintained with intravenously given lanatoside C. The urine output remained good. An electrocardiogram showed paroxysmal nodal rhythm with nonspecific T-wave changes. Levarterenol bitartrate, 20 mg. in 1,000 cc. of 5% glucose solution given intravenously, was necessary during the morning to maintain the blood pressure level. An additional 1,000 cc. of sodium chloride solution and 1,000 cc. of 5% glucose solution, each containing 100 mg. of hydrocortisone, were given during the day. In midafternoon administration of the levarterenol bitartrate solution was discontinued and the patient removed from the oxygen tent. The blood pressure remained at a normal level, and she experienced no respiratory difficulty.

On the fifth hospital day the patient felt well. She was taking fluid and food by mouth. The blood pressure was 115/72 mm. Hg, pulse 78 per minute. There were a few medium moist rales at the right lung base. All intravenous medication was discontinued. Therapy with orally given cortisone, 75 mg. four times daily, was begun and a digitalis preparation for oral administration substituted for the lanatoside C. The patient continued to show rapid improvement, and all signs of fluid retention disappeared. On March 20, 1955, therapy with all antibiotics and the digitalis was discontinued. On March 23, 1955, the cortisone dose was decreased to 75 mg. three times daily. Repeat chest x-ray showed almost complete clearing of the pulmonary infiltration. The patient was discharged from the hospital on March 26, 1955.

The patient was seen at frequent intervals after discharge, and over a period of five weeks the cortisone dosage was gradually reduced to 25 mg. given twice daily. Attempts to reduce it further resulted in a flare-up of joint symptoms. Eleven weeks after discharge from the hospital, her only medication was with cortisone and small amounts of acetylsalicylic acid. A general physical examination revealed blood pressure averaging 115/75 mm. Hg and no abnormalities except for moderate joint deformities due to chronic rheumatoid arthritis. Chest x-ray and electrocardiogram were normal.

Comment

That serious adrenal cortical insufficiency can occur during long-term cortisone treatment has been emphasized by many investigators. In the case reported here, it appears that the added stress of pneumonia, with its increased demands on the adrenal cortex, precipitated the acute situation in the same manner that a patient with adrenal cortical hypofunction develops a crisis if the substitution therapy is not increased during the period of stress.

Septicemia, producing a Waterhouse-Friderichsen type of adrenal insufficiency, must be considered as a diagnostic possibility in this case. Such an occurrence seems unlikely. A blood culture was sterile, no petechiae were observed, and adequate penicillin was administered approximately 11 hours prior to the onset of the acute episode.

Acute adrenal cortical insufficiency requires immediate treatment. With any type of adrenal cortical hypoplasia one cannot expect the administration of corticotropin to have a rapid effect. In patients who have received cortisone for long periods, it is usually expected that there will be a delay of a few days before corticotropin can cause any increase in the output of adrenal cortical hormones.[4] For this reason, replacement therapy with large doses of adrenal cortical hormones is indicated. The vasopressor agents are of value in the treatment of the immediate hypotensive episode.

In patients on long-term cortisone treatment, every infection should be looked upon as a potentially serious complication. Since resistance to infection is decreased by cortisone, an antibiotic or chemotherapeutic agent suitable for the specific infection should be employed early and in adequate doses. In addition, the dose of cortisone should be increased to compensate for the added stress. Similar precautions would also seem to be warranted in patients on prolonged corticotropin treatment. Several programs have been outlined for the prevention of adrenal cortical insufficiency in surgical patients on long-term adrenal steroid therapy.[8] These programs apply equally well to patients who develop infections while on long-term adrenal steroid treatment.

Summary

A patient under prolonged cortisone treatment developed acute adrenal cortical insufficiency shortly after the onset of pneumonia. Recovery occurred after intensive treatment utilizing vasopressor agents, large doses of hydrocortisone given intravenously, cortisone, and desoxycorticosterone acetate. Infection precipitating serious adrenal cortical insufficiency may occur in patients on prolonged adrenal steroid therapy.

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MASSIVE HEMORRHAGE OCCURRING DURING BRONCHOSCOPY

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and

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Massive hemorrhage occurring as a complication of bronchoscopy is fortunately an uncommon occurrence. However, it does occur and usually ends fatally in a very few minutes. Reports of these accidents and a method of management are not found readily in the recent American literature. Since these accidents will probably continue to happen, the following case is reported as an example of management that may allow one to treat similar cases satisfactorily.

Report of a Case

A 67-year-old man was admitted to the Veterans Hospital complaining of upper abdominal distention and pain. After thorough investigation, the diagnoses of hereditary hemolytic anemia, cholelithiasis, and symptomatic emphysema of the lung were made. Atelectasis of the left lower lobe was demonstrated by radiographic study. Due to the possibility of an obstructing malignant lesion, diagnostic bronchoscopy with topical anesthesia was recommended.

The left main stem bronchus below the orifice of the upper lobe was found on examination to be reddened and swollen to a degree sufficient to obstruct it almost completely. Taking of a biopsy specimen from this area was followed by occurrence of severe hemorrhage. The blood was dark and not under high pressure but flowed from the bronchoscope in a steady stream in such quantity that suction was ineffective in maintaining a clear airway. The patient's blood pressure at this time was within normal range, although the blood loss was continuing. The patient rapidly became cyanotic. Respirations were labored and then absent. At this time the bronchoscope was removed and an endotracheal tube with an inflatable cuff was inserted into the trachea as far as possible and the cuff inflated. Artificial ventilation by manual compression of the anesthesia bag filled with oxygen was started, and this was alternated with suction through the tube for cleansing of the lower respiratory tract.

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This tube was deliberately inserted into the right main stem bronchus. Coincident with the endobronchial catheterization, an incision was made in the left anterior chest and the left pulmonary hilus grasped by the surgeon to stop the bleeding. These procedures were followed by a cessation of bleeding from the mouth, a return of the patient's color toward normal, and a resumption of responsiveness by the patient to the extent that light ether anesthesia was required to allow further therapy. Blood was given rapidly. With the bleeding stopped by digital pressure and the airway adequately maintained, time was available for institution of sterile technique and reevaluation of the problem at hand. A definite bleeding point could not be found in the thorax. Frozen section of questionable areas within the thorax gave no positive evidence of carcinoma. Because of the patient's preoperative pulmonary symptoms, it was felt all attempts to save the lung were in order. However, hemorrhage rapidly recurred when the digital pressure was released. Therefore, pneumonectomy seemed indicated and was accomplished. The patient was kept anesthetized with ether throughout this procedure, and frequent cleansing of the lower respiratory tract

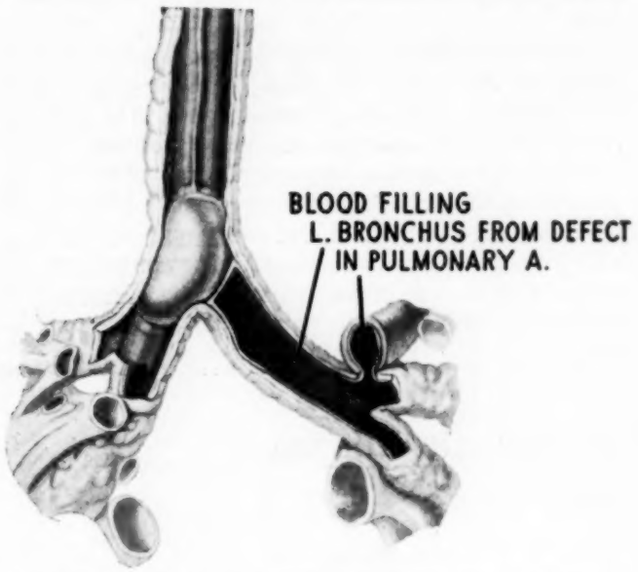

Diagram showing intubation of right main stem bronchus preventing contamination of the nonbleeding side with blood and providing adequate lumen for airway and suction.

was done by suction and intermittent irrigation with small amounts of saline solution. A total of 14 pt. (6,625 cc.) of blood was given to replace the loss.

Postoperatively, it was felt tracheotomy was indicated because of severe glossal edema and need for continued thorough cleansing of the respiratory tract. At the conclusion of the procedures, the patient appeared to be in very satisfactory condition. His condition continued satisfactory except for oliguria and mild dyspnea for three days. At the end of the third day, he became less alert and febrile and developed hypotension and tachycardia. He died 80 hours postoperatively. Autopsy revealed a severe congestion and consolidation of the right lung. A large amount of black fluid similar to that found in the stomach was found in the tracheobronchial tree. The lesion of the left lung was found to be bronchiectasis.

Comment

Although this patient eventually died, it is felt that a person treated similarly without the complication of anuria and severe disease of the other lung might survive. Death in these patients probably is due to asphyxiation rather than hemorrhagic shock. For this reason, treatment was first directed toward establishing a clear, maintainable airway. This was accomplished by using the technique of endobronchial intubation with a cuffed endotracheal catheter. The advantages of this technique

over packing with some form of compressible material are rapidity and ease of introduction, lack of interference with airway while being performed, and facilitation of cleansing of airway immediately and intermittently for an indefinite period of time. The inflated cuff may or may not act as a tamponade to help in hemostasis.

The endotracheal tube can be inserted into either the bleeding or the nonbleeding side. If passed into the bleeding side, the cuff could be inflated, the upper end of the tube clamped, and ventilation accomplished by use of a mask over the face. In this circumstance, suction and cleansing of the respiratory tract on the nonbleeding side is not facilitated. Cleansing of the nonbleeding side is important because aspiration will invariably occur. This phase of the management can be accomplished by anyone capable of inserting a bronchoscope with the use of equipment that should be standard in any operating room.

The thoracotomy was done with no attempt at sterile technique and with no anesthesia, with the same urgency one would use in treating cardiac arrest. The rapid accomplishment of hemostasis and ventilation then allowed time for deliberation as to proper therapy. In this case, pneumonectomy was mandatory because no reparable vascular lesion was found, but adequate time was available for consultation and pathological examination. The cause of death was probably anuria and pulmonary insufficiency subsequent to pneumonia in the remaining lung.

AGAMMAGLOBULINEMIA

REPORT OF A CASE

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Although a diminution of serum gamma globulin or even its total absence electrophoretically not infrequently follows an infection in early childhood, it is much less common in adults. A persistent diminution or absence of serum gamma globulin as the cause of multiple infections is a concept that was introduced by Bruton [1] in 1952. The syndrome in adults seems to be very rare. Moncke,[2] using paper electrophoresis, found only one case of complete agammaglobulinemia, in a male aged 16, among 6,000 adults and adolescents above the age of 15. Because of the rarity of the condition, the following case in an adult is reported.

A 53-year-old female was admitted to the Lenox Hill Hospital on Oct. 28, 1954, with a pneumonitis of both lower lobes. This was her ninth hospital admission. The patient had been well until January, 1949, when she was operated upon for internal hemorrhoids and a rectal fissure. Her postoperative course was complicated by pneumonia, from which she completely recovered. The pneumonia recurred in May, 1949. After these illnesses, she had frequent episodes of chills, night sweats, cough productive of blood-streaked sputum, and nasal congestion; these were diagnosed as "bronchitis." In October, 1950, she developed mumps, and in December, 1950, she had herpes zoster of the left thorax. Early in March, 1951, she was treated for a pneumonitis complicated by pleurisy with effusion. On March 28, 1951, she was admitted to Lenox Hill Hospital for the first time, with a pneumonitis of the right lower lobe. Her second admission was on June 21, 1951, for phlebitis of the left greater saphenous vein and cellulitis of the left leg. Her third hospital admission was on Dec. 31, 1951, for an acute influenzal meningitis. Between these hospital admissions she had had numerous respiratory infections with high temperatures, constant nasal congestion, and a mild productive cough. In addition, she had suffered from a chalazion of the right upper eyelid, a purulent otitis media on the right, and an ulceration of the right leg with cellulitis.

After her discharge, she continued to have bouts of chills and high temperatures at irregular intervals. Her fourth admission was on May 21, 1952, for an acute pyelonephritis. In June, 1952, she had a superficial thrombophlebitis of the left ankle. Her fifth admission was on July 21, 1952, for a pneumonitis of the lower lobe of the left lung. Her sixth admission was on Aug. 11, 1952, for a pneumonitis of the lower lobe of the right lung and the left hilar region. On Sept. 13, 1952, she was admitted for the seventh time, with a second attack of influenzal meningitis and septicemia. In October, 1952, she had another episode of herpes zoster, this time involving the course of the right seventh cervical nerve. In December, 1952, continuous prophylactic antibiotic therapy was begun. Nevertheless, in May, 1953, she developed a pneumonitis of the lower lobe of the right lung. On Sept. 16, 1953, she was readmitted for a recurrence of the same condition. She was treated at home for pneumonitis of the lower lobe of the right lung in November, 1953, and for pneumonitis of the lower lobe of the left lung in April, 1954. Her ninth, and final, admission was on Oct. 28, 1954, for bilateral pneumonitis.

Sputum cultures during her numerous respiratory infections revealed the pneumococcus as the predominating organism, except on one occasion when Escherichia coli predominated. The latter was reported during a period of treatment with prophylactic doses of chlortetracycline. A positive blood culture for pneumococcus was reported on several occasions. Her attacks of pneumonitis were always associated with high temperatures, ranging from 104 to 106 F (40 to 41.1 C), chills, and blood-streaked sputum. Leukocyte and polymorphonuclear counts associated with these illnesses, however, were usually only moderately elevated. They ranged from 5,250 cells per cubic millimeter, with 67% polymorphonuclear leukocytes, to 16,750 cells, with 61% polymorphonuclear leukocytes. The count of 5,250 white blood cells was at a time when she was receiving prophylactic doses of chlortetracycline and the predominating organism in the sputum culture was Esch. coli. Both attacks of meningitis were due to Hemophilus influenzae, group B. Her temperature on admission with her first attack of meningitis was 106.2 F (41.2 C) and 105 F (40.5 C) on her second admission. The white blood cell counts on admission during both these illnesses were 23,200 per cubic millimeter, with 79% polymorphonuclear leukocytes, and 21,000, with 85% polymorphonuclear leukocytes respectively. The pyelonephritis was associated with Proteus vulgaris on urinary culture. However, she had been taking chloramphenicol (Chloromycetin) prior to admission.

An interesting feature of her many illnesses was the fact that, in spite of their severity, the erythrocyte sedimentation rates were never increased. They usually ranged between 1 mm. and 9 mm. in one hour, and on only one occasion did the rate reach 19 mm. (during her second attack of meningitis). Bronchographic examinations performed in April, 1951, and November, 1952, revealed no evidence of bronchiectasis. X-rays of the sinuses showed evidences of a chronic sinusitis involving the maxillary antrums and the ethmoids. Intravenous pyelograms revealed no abnormality of the genitourinary tract. X-rays of the gastrointestinal tract were negative, except for a small diverticulum of the pelvic colon.

Her first attack of meningitis was complicated by chronic purulent otitis media and mastoiditis. Because of the possibility of the latter acting as the focus for the meningitis, a simple mastoidectomy was performed. At the operation there was no sign of involvement of the venous sinuses or of extension to the

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dura mater. Cultures from the mastoid were sterile, and those from the middle ear antrum revealed a nonhemolytic Micrococcus (Staphylococcus) pyogenes var. albus. In the course of many of her acute infections, the spleen was reported as being palpable from one to three fingerbreadths below the costal arch.

Her infections responded promptly to antibiotic therapy. The treatment for her respiratory infections consisted of administration of penicillin, oxytetracycline, chlortetracycline, and chloramphenicol at various times, and she responded equally well to all of them. The influenzal meningitides were rapidly brought under control by streptomycin. The P. vulgaris pyelonephritis was treated with chloramphenicol and sulfisoxazole (Gantrisin).

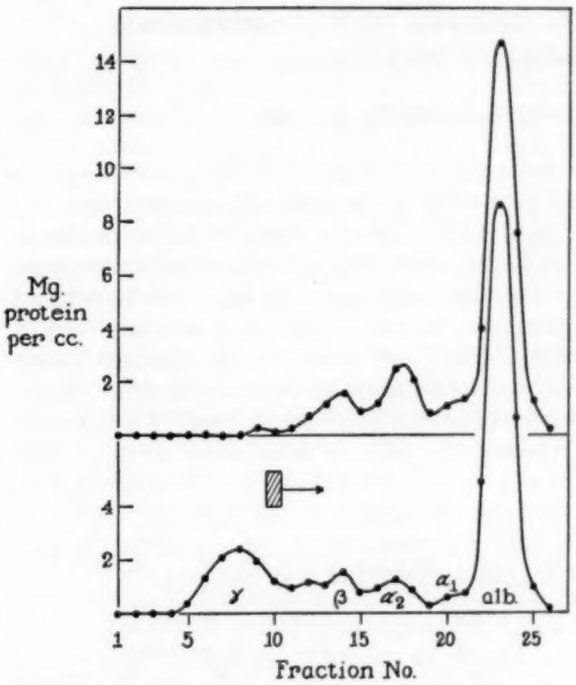
The patient's father died at age 55 years of a heart attack, and her mother died in diabetic coma at 65. One brother, aged 57, died of carcinoma of the lung. One sister, aged 56, has diabetes mellitus and hemiplegia. She has two children—one son, aged 34, and one daughter, aged 33—both living and well. There are three grandchildren all living and well. There is no history of repeated infections in any other member of the family, on either the maternal or the paternal side. The social history is not remarkable.

Before her ninth, and final, admission, the patient had been on prophylactic therapy with chlortetracycline, 200 mg. daily. Three weeks prior to admission, she noted increased productive cough with blood-streaked sputum. Her temperature had reached 104 F (40 C) for 10 days before admission. Examination at the time of admission revealed a well-developed, well-nourished female in no acute distress. There was slight dulness to percussion over the bases of both lungs; medium coarse rales and rhonchi were audible over the entire chest but were especially marked at the bases of the lungs. The liver was palpable one fingerbreadth below the costal arch, and the tip of the spleen was barely palpable. The patient's course in the hospital was uneventful. With an increased dose of chlortetracycline, 250 mg. every six hours, her temperature rapidly returned to normal, and she was afebrile during the remainder of her hospital stay. It was during this ninth admission that agammaglobulinemia as the cause of her multiple infections was investigated. Liver function studies showed the following results: total cholesterol 168 mg. per 100 cc., free cholesterol 78 mg. per 100 cc., esters 90 mg. per 100 cc., cephalin flocculation negative, thymol turbidity 3.0 units, alkaline phosphatase 4.5 Bodansky units, total protein 5.8 gm. per 100 cc., albumin 4.9 gm. per 100 cc., and globulin 0.9 gm. per 100 cc. Total serum protein determinations had been previously performed on Oct. 8, 1952, with the following results: total proteins 7.0 gm. per 100 cc., serum albumin 5.5 gm. per 100 cc., and serum globulin 1.5 gm. per 100 cc. A starch-zone electrophoresis (see figure) was performed by Dr. William J. Eisenmenger at the Rockefeller Institute Hospital and revealed a minimal amount of gamma globulin. Additional studies were as follows: tuberculin skin test negative; Schick test positive; febrile antigens negative; cold agglutinins negative; Wassermann negative; blood type group A, Rh_0 positive; glucose 100 mg. per 100 cc.; and urea nitrogen 8.2 mg. per 100 cc. The patient has since received 0.1 gm. of pooled human gamma globulin per kilogram at monthly intervals. The period of observation is too short to evaluate its effectiveness.

Comment

Since the nine cases reported by Bruton and coworkers [3] were all in male children, agammaglobulinemia at first appeared to be both sex-linked and congenital. In the short period of time, however, since the publication of these papers, cases of the syndrome in adults,[4] both male and female, have been reported. They have been in either adolescents or young adults, and it has therefore been tempting to ascribe the late onset of symptoms to environmental factors. The case reported above is of interest not only because it occurred in a female but also because it originated at the age of 47 in a person who had lived her entire life in the city. Her defect in gamma globulin synthesis is certainly an acquired one, and its pathogenesis is unknown.

The syndrome presented in our case is similar in all respects to those already reported in the literature. The main features are the multiple infections, the absence of antibodies and isoagglutinins, the response to antibiotics, the low sedimentation rate, and the low gamma globulin value in spite of a normal total serum protein level. Whether injections of gamma globulin in the amount the patient is now receiving (0.1 gm. per kilogram per month) will furnish protection against the numerous infections she has suffered in the past six years must await a longer period of observation. It will be noted that starch-zone electrophoresis of the patient's serum showed it to contain 43 mg. of gamma globulin. In most of the cases reported there has been a complete absence of this fraction, but the method used has been less sensitive than starch-zone electrophoretic separations. Immunochemical studies of the patient's serum, with antigamma globulin serum, gave a very weak precipitation. The increased A_2 fraction is probably secondary to the multiple infections, because it consists of mucoproteins, which increase markedly after such infections.



Patterns of starch-zone electrophoretic separations of serums from patient (upper) and a normal adult (lower) done simultaneously in diethylbarbiturate buffer pH 8.6,T/2=0.1. Box and arrow indicate sites of origin and anodal direction of migration. A striking decrease in the gamma globulin component of the patient's serum is apparent.

Summary

A woman, aged 53, with the typical findings of agammaglobulinemia, had been well until the age of 47. The course of her illness included numerous recurrent infections. Electrophoretic patterns of her serum showed an almost complete absence of gamma globulin.

Addendum

The patient has received 0.1 gm. of pooled human gamma globulin per kilogram at monthly intervals for the past three months. Except for minor upper respira-

tory infections, not associated with fever and for which she has been given short courses of oxytetracycline, she has remained perfectly well.

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GRIESS' NITRITE TEST IN DIAGNOSIS OF URINARY INFECTION

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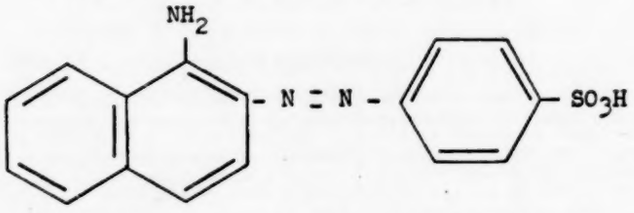
The nitrite reaction of Griess [1] has been used fairly extensively for testing of the purity of water supplies. The test is based on the demonstration of nitrite produced in contaminated water through the reduction by bacteria of nitrate naturally present in the water. In the field of microbiology, the nitrite reaction is an accepted procedure for the study of nitrite-forming bacteria grown on culture mediums to which nitrate has been added. The reaction consists of the development of a red color in the presence of nitrite by addition of an acidic sulfanilic acid-α-naphthylamine reagent. The reaction is highly sensitive and results in the formation of azo-α-aminonaphthalene-parabenzene-sulfonic acid.[2] The formula of the color compound is given below.



The nitrite reaction was discovered in 1879 by Griess, a German chemist, who employed a reagent consisting of sulfanilic acid and α-naphthylamine in dilute sulfuric acid. In his first publication Griess reported the occurrence of a positive nitrite reaction with human saliva, whereas negative reactions were consistently obtained with freshly voided urine specimens from normal individuals. In 1899 the nitrite test was modified by Ilosvay,[4] who substituted acetic acid for the dilute sulfuric acid used by Griess. This substitution resulted in an increased speed and intensity of the color development. The presence of nitrite in human saliva was confirmed by Ilosvay.[5]

The introduction of Griess' reaction into the field of clinical medicine for use in the diagnosis of urinary infection did not take place until 1922. The application of the test to urinary analysis seems to have been due mainly to the efforts of Weltmann.[6] During the subsequent years a limited number of clinical publications on the Griess method have appeared, chiefly in the German and Scandinavian literature. A more extensive study of the reaction was published recently by Bechgaard and Jansen,[7] based on the investigation of 1,700 urine samples. The nitrite reaction is mentioned briefly in several European textbooks on clinical chemistry [8] but is described in some detail only in a publication by Becher.[9] No reports on the clinical application of the test have so far appeared in the American literature. The purpose of the present review is to describe the procedure and to outline its usefulness as a laboratory method for the diagnosis of urinary infection.

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Procedure

Preparation of Griess' Reagent.—Sulfanilic acid solution, 0.5 gm. of sulfanilic acid (chemically pure) dissolved in 150 ml. of 10% acetic acid, is prepared.[9] The α-naphthylamine solution, 0.2 gm. of α-naphthylamine (chemically pure) dissolved in 20 ml. of distilled water, which has been heated to boiling, is prepared. After thorough stirring, the solution is filtered through filter paper. The combined nitrite reagent is prepared by adding the α-naphthylamine solution to the sulfanilic acid solution. The combined reagent is immediately ready for use. It should be stored in a dark flask.

Stability of Reagent.—The combined reagent after several weeks develops a pink color, which makes it unusable. The sulfanilic acid and α-naphthylamine solutions may be kept separately. Under such conditions the sulfanilic acid reagent remains stable, whereas the naphthylamine solution will turn progressively pink. Hallmann [8a] advises a means of regenerating the combined reagent after it has turned pink by shaking it vigorously with small amounts of metallic zinc powder. After filtration the reagent is again ready for use. The maintenance of the reagents in powder form has been suggested by Jaeggy and Lanz [10] for greater stability. In this modification, 6.2 gm. of α-naphthylamine, 1 gm. of sulfanilic acid, and 25 gm. of citric acid are mixed and ground in a mortar. The resulting powder is dried in an exsiccator and, after drying, is again ground in a mortar.

Test of Activity of Reagent.—The Griess reagent should be tested occasionally with a weak, freshly prepared solution of sodium nitrite in water.

Method of Testing of Urine for Nitrite.—A few milliliters of the freshly voided urine is placed in a test tube. To the urine sample is added one-fourth to one-half volume of the combined reagent solution. In the presence of nitrite, a red color develops nearly instantaneously and remains stable for several hours. It is unnecessary to decolorize the urine specimens with activated charcoal before the addition of the Griess reagent, as suggested by Varady and Szanto.[11] Moderate amounts of protein do not affect the reaction. The pH of the urine sample is not important, since an excess of acid is added with the Griess

reagent. Cloudiness of the specimen, if caused by precipitated phosphate, will disappear upon the addition of the strongly acid reagent.

Comment

In the majority of cases the urine of normal individuals contains a certain amount of nitrate, derived from the intake of vegetable foods. Under normal circumstances the urine contains no trace of nitrite. The demonstration of nitrite in the urine can therefore be considered as evidence for the presence of bacteria that reduce nitrate to nitrite as a phase of their metabolic activity. Not all of the bacteria encountered in urinary infections in human individuals are capable of reducing nitrate to nitrite. The most important of the nitrate-reducing micro-organisms is Escherichia coli. Micrococci (staphylococci) and Proteus vulgaris will also effect reduction of nitrate, but at a somewhat slower rate. The Salmonella group of bacteria are inconstant nitrate reducers. Of the micro-organisms incapable of reducing nitrate, the most significant are streptococci, gonococci, and tubercle bacilli. False-positive reactions with Griess' reagent are seen only under conditions in which urine samples are kept without aseptic precautions and thus subjected to airborne bacterial contamination. Even under such circumstances, maintenance of the temperature of the urine at 37 C for about eight hours is usually required for the reaction to become positive.

If a negative Griess reaction is obtained on a urine sample, the possibility that the urine is sterile or that the urine is contaminated by bacteria incapable of reducing nitrate to nitrite must be considered in the interpretation of the finding. Also, there is the possibility that the urine contains nitrate-reducing bacteria but that one of the following conditions may exist: 1. The reagent has deteriorated. Precautions to avoid this source of error have been outlined above. 2. The urine did not contain nitrate. Although the urine of the majority of the population contains nitrate, individuals are occasionally encountered who do not excrete nitrate in the urine. If under such conditions a few drops of a 10% sodium nitrate solution is added to the voided urine, nitrite will appear in the urine sample within one-half to two hours if the temperature of the specimen is maintained at 37 C. 3. The patient's micturitions are so frequent that the bacteria lack the necessary time to produce nitrite. In order to demonstrate the presence of nitrite-forming bacteria, the urine should be placed for two hours in the thermostat at 37 C. 4. The patient suffers from urinary retention. Under such conditions, the nitrite produced by the nitrate-reducing bacteria may be further decomposed by the same bacteria. This applies especially to Esch. coli. If a few drops of a 10% sodium nitrate solution are added to the voided urine specimen, formation of nitrite can be demonstrated after two hours with the temperature of the sample maintained at 37 C.

The above review of the application of the Griess reaction to urine samples demonstrates the importance of the method for the physician. The practical significance of the test is increased by the fact that Esch. coli, which is a strong nitrate reducer, is the organism most often encountered in urinary infections. It is of interest to point out that bacteriuria alone, without pyuria, also yields a positive nitrite test. The causes of error in the case of negative reactions can be disregarded for most practical purposes. The method is of such striking simplicity that nothing prevents it from being adopted just as routinely as tests for albumin and sugar have been for a long time. Without resorting to microscopic examination and urine culture, or before doing so, the practitioner will derive immediate and important information from the nitrite test.

If the physician encounters a case of cystitis associated with a negative nitrite test, suspicion of a tuberculous infection of the urine must be entertained, although streptococci, too, fail to produce nitrite. One will have to bear in mind that a positive Griess test does not rule out the existence of a mixed infection, caused, for instance, by a combination of a nitrite-reducing species and Mycobacterium tuberculosis.

It is not my intention to imply that the Griess nitrite test in all cases can replace urine culture on appropriate mediums or animal inoculation. Apart from the immediate and reliable information afforded by the test, the Griess reaction may occasionally yield information that serves to correct results obtained by urine culture. An example of this kind is reported by Weltmann and Haslinger,[12] who obtained a culture of micrococci from a urine specimen that gave no color reaction with the Griess reagent. This discrepancy pointed to an extraneous contamination of the culture medium, a contention that was confirmed through culturing of a new urine sample from which no organisms were grown. The assistance afforded by the Griess reaction in assessing antibacterial treatment of urinary tract infections is obvious and requires no further comment.

Summary

The Griess reaction for qualitative nitrite determination and for the diagnosis of urinary infection, because of its simplicity and reliability, deserves to be used as a routine test for diagnosis of urinary infection in office and hospital laboratories.

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COUNCIL ON FOODS AND NUTRITION

Report to the Council

The following paper was presented at the symposium, "Some Inorganic Elements in Human Nutrition," in Nashville, Tenn., April 4, 1955. This symposium was sponsored jointly by the Nashville Academy of Medicine, the Vanderbilt University School of Medicine, and the Council on Foods and Nutrition. This report is the second of the series, the first of which appeared in THE JOURNAL *April 21, 1956.*

EUGENE H. STEVENSON, M.S.
Acting Secretary.

COPPER METABOLISM IN MAN

Clark J. Gubler, Ph.D., Salt Lake City

Copper as a remedy for various ailments has been of interest to physicians for many hundreds of years. It was first recognized as a normal constituent of human blood in 1875,[1] but it was not until 1924 that Elvehjem and coworkers demonstrated the essential nature of copper in mammalian nutrition, particularly in erythropoiesis.[2] Although a considerable amount of work has been done since, there are still many gaps in our knowledge of what copper does in the body. This report is a summary of our present knowledge of the metabolism and physiological functions of copper. Studies of a fundamental nature on copper metabolism in man are relatively few; therefore, much of our information must of necessity be drawn from experiments with animals.

Absorption and Excretion

Copper is widely distributed in foods, the amount depending upon the copper in the environment. The average adult ingests 2.5 to 5 mg. of copper per day, but he will maintain copper balance on an intake of approximately 2 mg. of copper per day.[3] It is difficult to find a diet sufficient in calories that does not supply at least 2 mg. of copper per day. The requirement is greater during pregnancy to provide the stores necessary for the fetus, but whether this must be met by a greater intake or by more efficient retention of copper is not known. Children probably require about 0.05 to 0.1 mg. of copper per kilogram of body weight per day.[1]

Because of the technical difficulties involved in carrying out copper balance studies, little is known of the factors governing the absorption of dietary copper. It is quite likely that it is not regulated in any manner analogous to the regulation of iron absorption. In contrast to iron, copper balance is accomplished by an adjustment of the excretion rate to accommodate the amount of copper absorbed. (This may be true only within certain limits, since an excessive retention seems to be possible with a high intake of copper.) Substances in the diet that form insoluble or slightly dissociable complexes with copper exert an inhibitory effect on its absorption. The form in which the copper is ingested also undoubtedly influences the degree of absorption.

Normally, an insignificant amount of copper is excreted in the urine, 0 to 70 mcg. per day. The amount is largely independent of the intake and is not greatly influenced by the route of administration of the copper. Of that excreted after injection or ingestion, 99% is excreted by way of the stools; after ingestion the greater part of the stool copper represents unabsorbed copper.[4] Of small (1 mg.) doses of copper given orally and labeled with radioactive copper (Cu^{64}), 30% to a maximum of 40% was absorbed. Studies in dogs indicate that the main route of excretion of copper, once it has entered the body tissues and fluids, is through the liver by way of the bile (table 1).[5] If the bile flow is obstructed, there is a tendency for a greater net retention of copper. The data available suggest that excretion of copper in man follows this same pattern.[6] A small fraction of the copper is excreted directly through the intestinal wall; in dogs, this amount represents 13 to 15% of the total excretion.[4]

TABLE 1.—*Excretion of Intravenously Administered Radioactive Copper by Dogs*

Group	Dogs, No.	Injected Cu^{64} Excreted, %		
		Urine	Stool	Total
Control	3	0.6	8.4	9.0
Bile duct ligated	3	2.8	3.2	6.0
Bile duct transposed to urinary bladder	3	10.8	1.5	12.3

Storage

The body of an adult contains about 100 to 150 mg. of copper.[1] The liver is not only the chief organ of excretion, as already noted, but also the chief organ of storage as illustrated in figure 1. When Cu^{64} is given intravenously, external counts taken over the area of the various organs show that the liver takes up the greater proportion of the copper. The liver and the central nervous system contain the highest copper concentration of any organs of the body; the spleen, muscles, and bones contain the lowest. Because of their great total mass, however, the muscles and bones contain a large part (50 to 75%) of the total body copper. The copper content of fetal liver is 5 to 10 times greater than that of the liver of the normal adult in both man and animals. This may be a provision to tide the infant over the period when the diet consists chiefly of milk, which is notably low in copper. It requires 5 to 15 years for the level of copper in the liver of normal human infants to drop to the adult level.[1]

We know very little of the form in which copper is stored in the body. Several liver copper-proteins have been isolated[7] in amounts representing such a small proportion of the total copper that it is difficult to say whether they represent normal storage forms of copper or some specific fraction of the liver copper.

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Transport

Blood contains a small but characteristic amount of copper that is normally distributed nearly equally between the plasma and the red blood cells. Normal plasma contains an average of 116 mcg. of copper per 100 ml., with a range of 68 to 161 mcg. for different persons. The

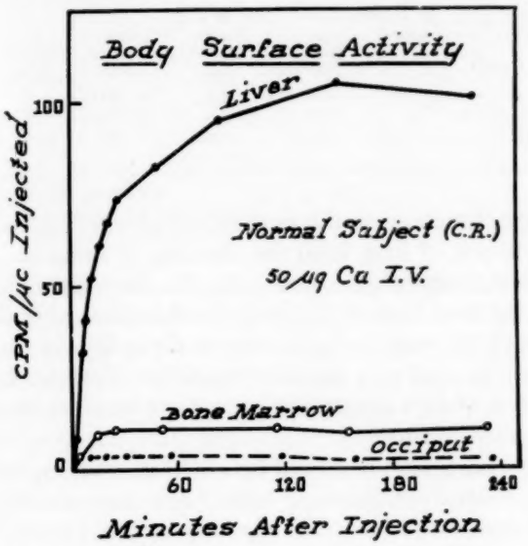

Fig. 1.—Uptake of radioactive copper by the liver, bone marrow, and occiput of a normal person. (Modified from Bush and others.[4])

plasma copper level remains remarkably constant from day to day or from week to week and exhibits no diurnal variation as does the level of plasma iron.

Plasma copper is composed of two fractions, a loosely bound fraction accounting for about 5% and a firmly bound fraction representing 95% of the total.[8] The firmly bound fraction, or "indirect-reacting" fraction, is bound to an a_2-globulin and is called ceruloplasmin.[9] This copper protein has a copper content of 0.34% and a molecular weight of 151,000. The loosely bound fraction may be preferentially bound to albumin, but under certain conditions it may also bind nonspecifically with other plasma proteins.[10] This fraction will react directly with the copper colorimetric reagent sodium diethyldithiocarbamate, at slightly alkaline pH, without previous splitting off with acid, as is necessary with the a_2-globulin bound copper. Hence, the term "direct-reacting copper" has been applied to the loosely bound fraction.

Plasma copper increases in a variety of pathological conditions (table 2) and in pregnancy (fig. 2),[11] but the physiological significance of these changes is not understood. Red blood cell copper is not greatly altered in these conditions. Increase in plasma copper is chiefly due to an increase in the ceruloplasmin or indirect-reacting fraction (in figure 3, the ceruloplasmin level, as determined immunologically, is compared with the indirect-reacting copper). This suggests that both determinations measure essentially the same copper fraction.

Ceruloplasmin possesses enzymatic activity as a polyphenol oxidase,[12] and there is a good correlation between the oxidase activity of plasma and the ceruloplasmin level (fig. 4). The physiological function of ceruloplasmin is not known, nor is it known whether or not the polyphenol oxidase activity is of any physiological significance.

Copper is transported by the direct-reacting fraction, regardless of whether copper is injected, administered orally, or added in vitro to the plasma. When Cu^{64} is administered orally or intravenously, it appears first in the albumin fraction and later (4 to 6 hours) in the

TABLE 2.—*Plasma and Red Blood Cell Copper in Pathological States and Pregnancy*

Condition	Plasma Copper, Mcg./100 Ml.		Red Blood Cell Copper, Mcg./100 Ml.	
	Subjects, No.	Mean + Standard Deviation	Subjects, No.	Mean + Standard Deviation
Normal	..	116	..	115
Pregnancy	30	222±38	11	130±30
Infection	38	167±35	18	116±34
Acute leukemia	21	236±79	5	98
Chronic leukemia	22	148±31	12	101±39
Hodgkin's disease	14	171±58	8	109
Hemochromatosis	14	134±24	..	.....
Pernicious anemia	11	121±36	2	98

globulin fraction after it has been incorporated into ceruloplasmin. In persons having a high plasma copper level, the rate of incorporation of Cu^{64} into ceruloplasmin is increased.

The normal red blood cell copper level is about 115 mcg. per 100 ml. of packed red blood cells. Current studies of the transfer of Cu^{64} between erythrocytes and plasma suggest that the red blood cell copper is also made up of at least two fractions, a labile and a stable fraction. The labile fraction appears to be in equilibrium with the direct-reacting fraction of the plasma copper. Copper in the ceruloplasmin fraction of plasma will not transfer into red blood cells. Conversely, only a small fraction of

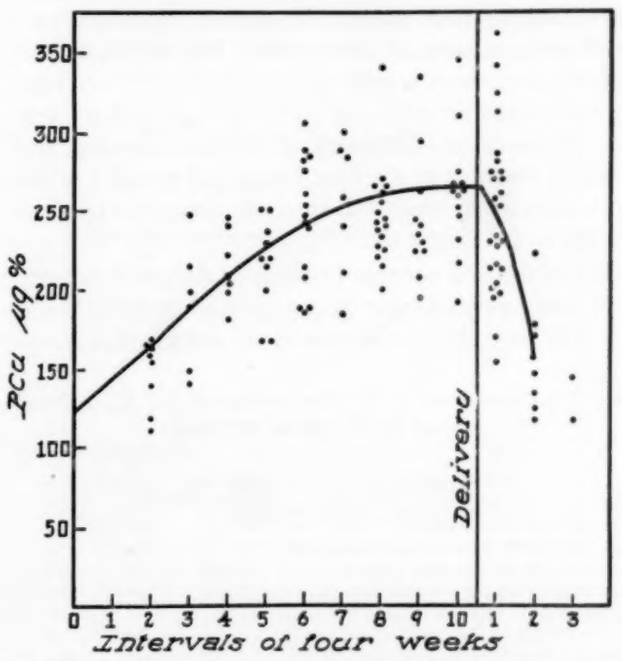

Fig. 2.—Plasma copper (P Cu) during pregnancy and the postpartum period. (From Fay and others, *J. Clin. Invest.* **28**: 489 [May] 1949.)

the firmly bound or stable fraction of red blood cells will transfer into plasma in vitro. Copper added to red blood cell suspensions in vitro first goes into the labile fraction of the red blood cell and then later (18 to 24 hours) is converted into the stable form. In some circumstances

the red blood cells may serve to transport copper in the blood; however, the physiological functions of the red blood cell copper are entirely unknown.

Copper Deficiency in Animals

One of the classic methods for studying the essential nature and functions of a substance is to produce a deficiency of the substance and then observe any changes

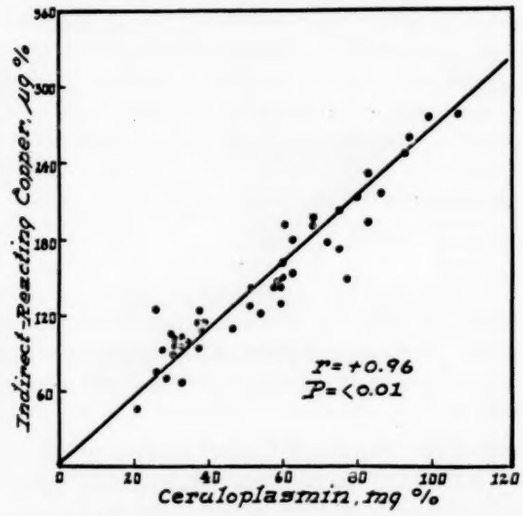

Fig. 3.—Relation between the indirect-reacting fraction of serum copper and ceruloplasmin for normal persons, pregnant women, and patients with infection, the nephrotic syndrome, and neurological disease. The diagonal line was plotted by the method of least squares; *r* refers to the correlation coefficient; *P* refers to the probability of such a correlation occurring by chance. (From Markowitz and others.[8b])

in function and metabolism. This method has proved fruitful in the case of copper. Earlier studies that demonstrated that copper is essential for normal erythropoiesis [2] have been confirmed by later work.[11] The rate of growth in copper deficiency is only moderately reduced until the terminal stages. In dogs and pigs, derangements in bone structure, such as shortening of the legs, bowing, and increased fragility of the long bones and nodules at the joints, have been observed. In some cases, the result is inability to stand or walk.[13]

One of the first changes to occur in copper deficiency is the early development of a profound hypocupremia. This is followed by a reduction in the red blood cell cop-

TABLE 3.—*Comparison of the Hematological and Biochemical Values in the Blood of Pigs*

Determination	Control	Deficient in Copper	Deficient in Iron
Volume, packed red blood cells/100 ml.	42	22	21
Mean corpuscular volume (µ³)	56	39	36
Mean corpuscular hemoglobin concentration, %	33	29	28
Red blood cell copper, meg./100 ml.	110	67	110
Mean corpuscular copper, meg./100 ml.	61	26	39
Plasma copper, meg./100 ml.	186	15	207
Plasma iron, meg./100 ml.	175	38	30
Total iron-binding capacity, meg./100 ml.	511	628	864
Bone marrow morphology	Normal	Normoblastic hyperplasia	Normoblastic hyperplasia

per level, a decrease in plasma iron to hypoferremic levels, and an increase in the iron-binding capacity of the plasma.[11] In pigs and rats, a profound anemia develops, which is microcytic and hypochromic and is associated with normoblastic hyperplasia of the bone marrow. In dogs, the anemia was found to be normocytic and normochromic.[14] The anemia in pigs deficient in copper resembles in most respects the anemia associated with iron deficiency,[11] as shown by table 3. These findings suggest

TABLE 4.—*Iron Content of Tissues After Oral Administration of Radioactive Iron to Pigs*

Group	Pigs, No.	Administered, Mg.	Recovered, Mg.	Recovery, %
Control	1,227	878	53	6
Deficient in copper *	1,230	1,416	27	2
Deficient in iron	1,231	1,245	23	2

* In red blood cells plus liver, spleen, kidney, and heart.

that copper functions in the metabolism of iron. Indeed, the absorption of iron from the intestine is reduced in copper deficiency (fig. 5 and table 4). In copper deficiency the total iron of the body per kilogram of body weight is of the same order of magnitude as that in iron deficiency, in spite of a high dietary intake of iron. This dependence of iron absorption on copper has also been demonstrated in rats.

In this connection it should be noted that synergistic or antagonistic relationships have been demonstrated between a number of the trace metals in animal nutrition. For example, an antagonism between molybdenum and copper and zinc and copper has been demonstrated. When high levels of molybdenum or zinc are present in the diet, even in the presence of normal copper levels, a copper deficiency may develop. This results from an impairment in absorption or in utilization of copper or both.

Poor iron absorption, however, is not the direct cause of the anemia in copper deficiency. Parenteral administration of massive amounts of iron to swine deficient in copper fails to prevent or alleviate the anemia; hence, a

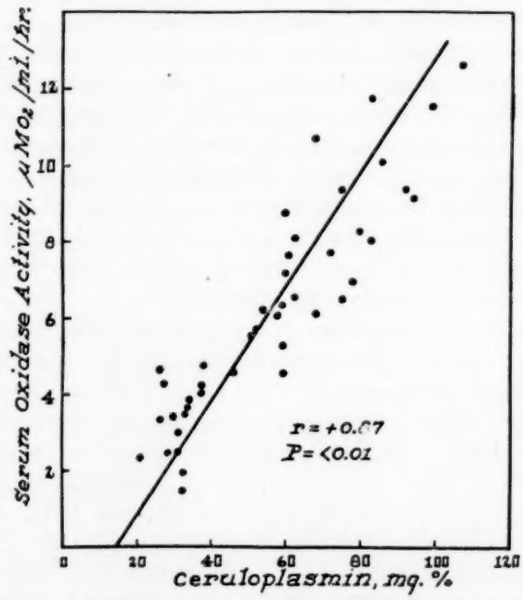

Fig. 4.—Correlation between serum oxidase activity and ceruloplasmin. The diagonal line was plotted by the method of least squares; *r* refers to the correlation coefficient; *P* refers to the probability of such a correlation occurring by chance.

deficiency of copper results in a failure to utilize iron for hemoglobin synthesis. Later work has shown that the bone marrow deficient in copper produces red blood cells

with a shortened survival time (table 5).[15] Although the plasma iron turnover rate is increased, the rate of incorporation of iron into hemoglobin is essentially the same as in normal unstimulated marrow. Whereas the normal bone marrow can increase its productive capacity about fourfold under stress, the bone marrow deficient in copper is incapable of increasing its capacity for red blood cell production. Hence, the anemia results from the shortened survival time of the erythrocytes and a limitation in the capacity of the marrow to produce new cells. As shown by red blood cell survival studies in pigs with radioactive chromium (Cr^{51}), the defect in the red blood cells deficient in copper can be at least partially corrected by injection of the red blood cells into normal animals (table 5).

TABLE 5.—*Survival of Red Blood Cells Tagged with Radioactive Chromium in the Pig*

Donor	Recipient	Pigs, No.	Mean Time, Half-Days	Life Span (Calculated Days)
Normal	Normal	4	17±3.6	64
Deficient in copper	Deficient in copper	10	9±1.9	33
Normal	Deficient in copper	4	16±3.6	58
Deficient in copper	Normal	5	13±2.2	49
Deficient in iron	Deficient in iron	3	18±4.2	69

Copper Deficiency in Man

It is still a controversial question whether copper deficiency has occurred or can occur in man. It is doubtful that an unquestioned case of copper deficiency has been reported in man. It is also extremely unlikely that copper deficiency could occur in normal humans even on suboptimal diets.

Since the plasma copper level is one of the most sensitive indexes of copper deficiency, a survey for hypocupremia was made in several human disorders in which copper deficiency might be expected to occur (table 6). In none of these cases was hypocupremia found in spite of the marked inadequacy in other nutrients of many of the diets. In fact, in some instances hypercupremia was found.

TABLE 6.—*Plasma Copper Level in Various Forms of Nutritional Deficiency*

Condition	Patients, No.	Mcg./100 Ml. Mean	Mcg./100 Ml. Range
Normal	228	116	68-161
Cirrhosis	7	136	101-159
Scurvy	2	169	155-183
Malnutrition *	38	148	92-215
Iron-deficient adults	9	132	102-164
Iron-deficient infants	26	168	117-225
Milk diet	2 †	143 ‡	109-178
Nutritional hypoalbuminemia	1	155	.....

* Repatriated American prisoners of World War II.
† Fed a milk diet low in copper for 4 and 5 mo. respectively.
‡ At the end of the experimental period.

Two mentally defective infants were placed for periods of 4 and 6 months on a milk diet such as is used in producing copper deficiency in animals. At no time could hypocupremia or anemia be demonstrated. The difficulty in producing copper deficiency in normal human subjects may be because the requirements for copper are less than those of animals or because the retention of available copper is more efficient.

As shown in table 7, normal plasma copper values in the newborn infant are lower than in the adult. Since the stores of copper are high in the fetus and newborn infant and the high levels persist for several years, it is not likely that this low value could be caused by a deficiency of copper; it may be caused by an inability of the fetal liver to produce ceruloplasmin at the same rate as does the liver of the normal adult. Low plasma copper, which is likewise probably caused by an inability to produce ceruloplasmin at a rate sufficient to maintain a normal level in the plasma, was found in a patient with idiopathic hypoproteinemia.

TABLE 7.—*Hypocupremia Associated with Various Conditions*

Condition	Cases, No.	Plasma Copper, Mcg./100 Ml. Mean	Plasma Copper, Mcg./100 Ml. Range
Newborn infant	14	75	45-110
Nephrotic syndrome	16	64	20-96
Hepatolenticular degeneration	8	51	33-71
Sprue	4	63	16-139
Idiopathic hypoproteinemia	2	66	60-72

A condition in which hypocupremia is quite consistently encountered is hepatolenticular degeneration (Wilson's disease). The hypocupremia associated with this disease is not caused by a deficiency of copper since the body stores are 10 to 30 times those of normal persons. There is a relatively greater reduction in ceruloplasmin than in the total plasma copper, with a resultant increase in the loosely bound, direct-reacting fraction. This is associated with an increased excretion of copper in the urine, probably as a complex with amino acids and peptides and not as ceruloplasmin. Hence the low plasma copper level is the result of a relative inability to synthesize ceruloplasmin rapidly enough to maintain normal plasma levels, and not because of an excessive loss of ceruloplasmin. The increased tissue levels probably result chiefly from a greater absorption of dietary copper.

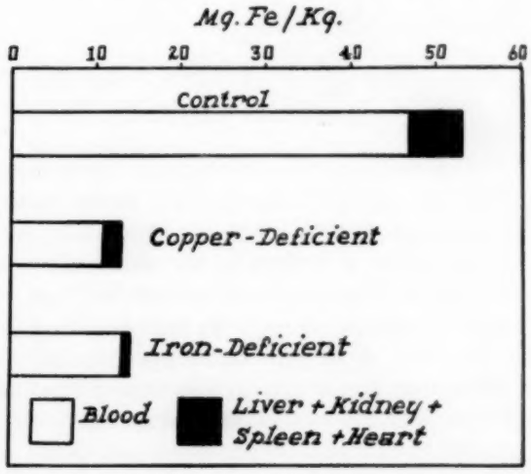

Fig. 5.—Total body iron and its distribution between blood and tissues in control swine, in those deficient in copper, and in those deficient in iron.

The possibility still remains of conditioned deficiencies of copper from conditions that cause a reduced absorption of copper or an increased loss from the body. Hemorrhage does not contribute significantly to loss of copper from the body, as it does in the case of iron, because of the low copper content of the blood.

The sprue syndrome is one condition in which a deficiency of copper might well be expected. One of three patients with this syndrome studied by this laboratory in collaboration with Dr. R. E. Hodges and coworkers of the University of Iowa presented several of the classic features of copper deficiency, namely, an extremely low plasma copper level (16 mcg. per 100 ml.), hypoferremia, microcytic hypochromic anemia, an increased plasma iron-binding capacity, and a low red blood cell copper level. Before the presence of a copper deficiency could be demonstrated by appropriate therapy, however, the patient began to respond during the base line period on the hospital diet alone. Another patient with sprue had a microcytic hypochromic anemia of long standing and also a low plasma copper level (63 mcg. per 100 ml.). A third, with no anemia, had

TABLE 8.—*Copper-Containing Proteins and Enzymes in Mammalian Tissues*

Protein	Molecular Wt.	% Copper	Substrate
Butyryl coenzyme A dehydrogenase	120,000-220,000	0.35	Saturated acyl coenzyme A derivatives of fatty acids (C4-C8)
Uricase	110,000	0.06	Uric acid
Tyrosinase	100,000 *	0.25	Tyrosine, dopa
Ceruloplasmin	151,000	0.34	Paraphenylene-diamine
Hepatocuprein	35,000	0.34	?
Hemocuprein (erythrocuprein)	(35,000)	(0.34)	?
Milk copper protein	?	0.19	?

* Values are for plant tyrosinase.

a normal plasma copper level. These preliminary observations indicate an area where further investigations may be profitable.

Another possibility of a conditioned copper deficiency is found in the nephrotic syndrome.[16] In this condition, reduced plasma copper levels are associated with increased excretion of copper in the urine. This is also accompanied by low plasma iron levels and low plasma iron-binding capacity, along with increased excretion of iron in the urine. Both iron and copper are excreted as the specific metalloproteins. It has been estimated that such patients lose 5% of their normal total ceruloplasmin per day. The low plasma copper (and iron) levels may be at least partially a result of an inability of the organism to synthesize these metalloproteins rapidly enough to meet the excretory loss. A depletion of stored copper and iron may also play a role. It remains for tissue copper and iron determinations to demonstrate whether or not this loss leads to a general depletion of tissue stores.

Although the possibility of a copper deficiency in humans does exist under certain conditions, it is not likely to be a common occurrence. Therefore, the widespread inclusion of copper in various antianemic preparations for clinical use is unnecessary.

Functions of Copper

Copper proteins present in mammalian tissues are listed in table 8. One of the latest to be described is butyryl coenzyme A dehydrogenase, the copper enzyme that catalyzes the first step in the oxidation of fatty acids with three to eight carbon atoms. This is the first dehydrogenase function that has been shown for a copper protein. Copper is linked with purine metabolism by the recent claim that uricase is also a copper protein.

The enzyme tyrosinase, which is likewise a copper protein, catalyzes both the oxidation of L-tyrosine to L-dihydroxyphenylalanine (dopa) and the further oxidation of dopa to melanin pigments. The pigmentation of the hair and skin in animals and man is undoubtedly dependent upon the activity of tyrosinase. The action of this enzyme causes the dark color of melanotic tumors. Tyrosinase also functions in the hardening and color of insect cuticle and in "ink" production in the squid and octopus.

Hepatocuprein, hemocuprein (erythrocuprein), and milk copper proteins have not as yet been shown to possess any enzymic or other activity of physiological importance. The plant polyphenoloxidases are also copper proteins. Although ceruloplasmin possesses polyphenol oxidase activity, no physiological function has been demonstrated for this enzyme. Ascorbic acid oxidase isolated from plants is a copper protein enzyme. Although it seems quite likely that such an enzyme might function in mammalian tissues in the oxidation-reduction of ascorbic acid, such an activity has not been observed.

The possibility still remains that copper is a part of or necessary for the activity of the cytochrome oxidase complex in mammalian tissues. If such is the case, this would place copper in a very fundamental position in the oxidation-reduction reactions and energy transfer of the cells. Copper has been repeatedly implicated in the oxidation of the glutathione of tissues. It has been shown, particularly in sheep, that copper is essential for the formation of normal wool. It catalyzes the closure of the sulfhydryl groups in the keratin molecule to form disulfide bridges necessary for the normal kinky structure of the wool fibers. Again, in ruminants only, copper has been found to play a role in the maintenance of a normal myelin sheath of the central nervous system. Copper is essential, either directly or indirectly, for normal bone formation although its exact function is not known. In copper deficiency the bones become thin and crooked and show a lack of normal trabeculation.

Summary

Copper is essential in mammalian nutrition; it is necessary for optimal absorption and metabolism of iron, for normal erythropoiesis, for bone formation, and for a number of oxidation-reduction reactions in tissues. Although copper deficiency has never been clearly demonstrated in human subjects, nevertheless, copper is undoubtedly essential for humans as well as for other animals and for plants.

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At the request of the Council, E. M. Nelson, Chief of the Division of Nutrition of the U. S. Food and Drug Administration, has prepared the following comments on a topic of current interest.

EUGENE H. STEVENSON, M.S.
Acting Secretary.

CONFERENCES ON ANTIBIOTICS

Two important conferences on antibiotics were held in Washington, D. C., during the fall of 1955. The first dealt primarily with the use of antibiotics in increasing the production of animals for food. The second reviewed the developments during the past year concerning the use of antibiotics in medicine.

Representatives from 15 foreign countries, including three from Russia, attended the International Conference on Antibiotics in Agriculture, which was sponsored by the National Research Council, Division of Biology and Agriculture. It was reported that the use of antibiotics to accelerate growth of poultry and swine is a well-established practice in the United States, resulting in an increase in food products from these sources. The visitors reported that in foreign countries the use of antibiotics in animal feed is increasing. Antibiotics have not been fed to ruminants because of the possibility of interfering with the processes of digestion in the rumen; however, further experience reported at the conference indicated that such a practice may prove feasible. Benefits have resulted from the feeding of certain antibiotics to dairy calves during the first two or three months of life, before the development of the rumen. Although the conference dealt chiefly with the use of antibiotics in animals, an interesting side light was that antibiotic supplementation failed to produce favorable growth response in a two-year study of Guatemalan children.

Extensive studies on the use of chlortetracycline as a preservative of meat, poultry, and fish were reported. It is of interest to note that on Nov. 30 the Food and Drug Administration announced that the use of chlortetracycline as a preservative for uncooked poultry would be permitted. The antibiotic is added to the water in which the poultry is chilled after it is dressed. A tolerance of 7 ppm of chlortetracycline was set for any portion of the uncooked poultry; cooking destroys the residue. This marks an important development in the processing of foods, the full significance of which will be determined only by broader experience.

The third annual Symposium on Antibiotics sponsored by the Food and Drug Administration reviewed all the developments in the uses of antibiotics during the past year. Papers on seven previously undescribed antibiotics and their possible use in medicine were read. Another interesting group of papers was concerned with the preservation of beef, sheep, and hog carcasses by intraperitoneal injection of oxytetracycline just before slaughter. Small residues remained in the tissue after treatment. A group of German workers gave a significant report on the lessened toxicity of streptomycin, neomycin, and viomycin when combined with pantothenic acid as a chemical compound or physical mixture. A method of reducing the toxicity of these drugs would be of great benefit and might well broaden their sphere of usefulness.

A panel discussion dealt with phenoxymethyl penicillin (penicillin V), a new biosynthetic penicillin that is suitable for oral use because it can survive the acid of the stomach. In another panel discussion, the opinion was expressed that a low level of penicillin in milk may cause a reaction in a sensitive person. The use of penicillin in the treatment of mastitis is believed to be responsible for the presence of a small amount of penicillin found in some samples of milk in a recent survey conducted by the Food and Drug Administration.

A sound basis for the growing trend of combining antibiotics with various therapeutic agents could not be found. Combinations of vitamins and antibiotics were among the first such products to come into use. After a searching review of the literature, it was concluded that the influence of vitamin nutrition on resistance to specific infections in man remains largely unknown. The paucity of information relative to the efficacy of antibiotic-vitamin combinations precludes any attempt to evaluate this method of therapy at the present time. There is a real need for carefully controlled experiments in a significant number of patients who have similar infections. The importance of maintaining adequate nutrition during the course of infections and many other diseases was emphasized, but much remains to be learned about what constitutes adequate nutrition.

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RESEARCH APPROACH TO ATHEROSCLEROSIS

GUEST EDITORIAL

Louis N. Katz, M.D.
Jeremiah Stamler, M.D.
and
Ruth Pick, M.D.

The field of arteriosclerosis has undergone phenomenal development in recent years, as witnessed not only by increasing interest and expanding research but also by significant achievements toward understanding the nature of the process. This is as it should be, for this entity is the number one killer of Americans, middle-aged as well as elderly. Today we recognize that atherosclerosis is the hub of the arteriosclerosis problem. Once atherosclerosis is conquered, a tremendous dent in morbidity and mortality rates will follow and the average life span will be greatly lengthened.

Progress in understanding has come first of all through rejecting the view that atherosclerosis is simply aging (senescence), which is inevitable and irreversible, and in accepting instead the idea that it is a disease and therefore preventable and (at least within limits) reversible; i. e., curable. The key to understanding the essence of the atherosclerosis problem lies in appreciating that it is basically a metabolic disease. In particular, alterations in cholesterol-lipid-lipoprotein metabolism play a critical and decisive (but not exclusive) role in the pathogenesis of atherosclerosis. Without alterations in cholesterol-lipid-lipoprotein metabolism, clinically significant atherosclerosis would occur but rarely (if ever), particularly in middle age, regardless of the functional state of the cardiovascular system. This fundamental theory of atherogenesis rests on an extensive foundation of research knowledge. It is documented by abundant data accumulated via the three major investigative approaches to unknown disease processes—the clinicopathological, epidemiological, and animal-experimental research methodologies.

Clinicopathological research, the oldest source of our knowledge concerning atherosclerosis, was first of all responsible for delineation of this condition as a distinct disease entity—a delineation achieved through the recognition that the unique, characteristic feature of the atherosclerotic plaque is its massive content of intracellular and extracellular cholesterol and lipids. This finding led to the earliest hypotheses concerning possible relationships of cholesterol to atherogenesis. Subsequent clinical studies showed that premature severe atherosclerosis is encountered with unusual frequency in several diseases; e. g., essential familial xanthomatosis, the nephrotic syndrome, myxedema, and diabetes mellitus, diseases apparently having no other feature in common except the supervention of prolonged periods of hypercholesterolemia. More recently, it has been definitely proved that any group of middle-aged patients with uncomplicated clinical coronary heart disease tends to have significantly higher levels of circulating cholesterol, lipids, and beta-lipoproteins than a comparable clinically normal control group. These clinical observations are strong pillars of support for the cholesterol-lipid-lipoprotein concept of atherogenesis.

Before discussing the specific contributions of epidemiological studies to our knowledge about atherosclerosis, a few preliminary words of general clarification concerning this methodology may be worthwhile. The entire medical profession is aware of the role of epidemiological research in solving problems of infectious disease, but the achievements of epidemiology are by no means limited to the conquest of contagious disease. A good example from recent American medical history is the elucidation by epidemiological research of the dietary causation of pellagra, "the hidden hunger." The focus of epidemiological research is not on patients but on the population at large. Its premise is that a great deal of information is obtainable from the study of disease in man, the species. Epidemiology poses such questions as: How does the incidence of a given disease; e. g., coronary heart disease, vary in time and space? Is it more frequent today than 50 years ago? Does it occur more in Americans than in British, Italians, Japanese, Chinese, Guatemalans, or Bantu? Is its incidence greater in American Negroes or whites, males or females, rural or city dwellers, laborers or professionals?

Most important of all, epidemiology asks: What new leads concerning etiology can be gleaned by dissecting out the factors responsible for observed differences in incidence of disease in different population groups? Hence, its focus on the human species in its natural environment. Man is of different ethnic origins, of two sexes, and of various ages. In the world today, and within the United States, man's biological and sociologic environment is extremely variable as regards climate, occupation, income, diet, housing, and mores. This is also true of earlier periods in man's existence. Data on these differences can be procured from archeological, anthropological, and sociologic studies. Field studies can supplement the information already available from these rich sources. Thus, analyses can go forward to ascertain if, for example, specific aspects of the mode of life (e. g., diet) account for patterns of incidence of disease. Epidemiology thus applied to the study of the so-called chronic degenerative diseases, among them

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atherosclerosis, is as yet a young and virgin field. It has pitfalls aplenty for the unwary. But it is vigorous, and has already made important contributions.

Epidemiological studies have shown that morbidity and mortality rates due to atherosclerosis, particularly coronary heart disease, vary markedly among different population groups. These variable patterns are almost certainly a result of differences in the mode of life of different peoples. Specifically, differences in life-span patterns of diet—particularly of cholesterol-lipid-calorie intake—have a key role in influencing the frequency of atherosclerotic disease. Apparently, the continuous assault of high-calorie, high-lipid, high-cholesterol intakes frequently overtaxes (and may alter) the organism's limited regulatory functions. Relative hypercholesterolemia and hyper-beta-lipoproteinemia tend to become established, facilitating cholesterol-lipid deposition and atherogenesis in the arteries. Hence, in countries where a diet high in cholesterol, lipids, and calories is habitually ingested, people frequently exhibit high levels of circulating cholesterol, lipids, and lipoproteins and a high incidence of atherosclerotic morbidity and mortality.

The contemporary American diet—a relatively recent innovation in nutrition, arising as a peculiar by-product of civilization in general and the socioeconomics of our culture in particular—places such a continuing strain upon the metabolic processes. This diet is pernicious to the cardiovascular system not only because of its excess in calories, lipids, and cholesterol (estimates indicate that the average American business and professional man ingests almost 60% of his total calories in the form of fats). It tends to be quite high in salt and in "empty" calories; i. e., calories derived from highly processed refined carbohydrates and fats (particularly animal fats and hydrogenated saturated vegetable fats), foods rich in energy but low in essential nutrients. Hence, the American diet, despite its high caloric level, is not infrequently inadequate, relatively or absolutely, in specific vitamins, essential fatty acids, minerals, and amino acids. It is this acquired "rich" and unbalanced diet that, by altering cholesterol-lipid-lipoprotein metabolism, creates the decisive prerequisites on a mass scale for the ready genesis of atherosclerosis in the American population. This is the dietary imbalance hypothesis on the relationship of nutrition to altered cholesterol-lipid-lipoprotein metabolism in atherogenesis.

These basic conclusions from epidemiological research do not mean that atherosclerosis is merely a problem of diet, pure and simple. In order to appreciate the unsoundness of such an oversimplified, one-sided concept, all that is necessary is to consider a large group of middle-aged American males, say age 40, 50, or 60, who over the life span have been "exposed" to a typical American diet high in cholesterol, lipids, and calories. Despite essentially identical patterns of food consumption, only a certain percentage of individuals in each of these groups would exhibit demonstrable clinical signs of coronary heart disease, although over 90% would have gross anatomic evidence (if autopsy were done) of significant coronary atherosclerosis. Thus, the same diet elicits widely differing lipid metabolic and atherogenic responses in different individuals of the "exposed" population group. Clearly then, "everything" cannot be "explained" by diet.

Further, in defiance of any pure-and-simple dietary explanation of atherosclerosis, two relatively homogeneous population groups, ingesting a similar potentially atherogenic diet over the life span, will differ significantly in susceptibility to clinical coronary heart disease depending on degree of physical activity. Habitually sedentary workers apparently tend to be victimized more frequently than their socioeconomic counterparts doing heavy work. Finally, a decisive feature of the epidemiology of coronary atherosclerosis in the United States is the sex differential; i. e., the marked susceptibility of the middle-aged male in contrast to the marked resistance of the middle-aged female—a phenomenon that can hardly be attributed to differences between the sexes in dietary patterns, since significant differences are apparently nonexistent.

What then is a valid theoretical formulation of the role of diet? Present knowledge warrants the following concept: The ingestion over the years of an unbalanced diet rich in cholesterol, lipids, and calories is an essential prerequisite for the development of significant atherosclerosis in a sizable proportion of a population group. In such a population group, habitually "exposed" to this potentially atherogenic diet, given individuals may or may not be victimized at any given age, depending apparently upon the interplay of a multiplicity of additional contributing and counteracting factors; e. g., genetics, heredity, sex, physical activity, fatigue, stress, other metabolic disease (diabetes), and local factors (vascular trauma and/or infections).

Knowledge derived from animal experimentation is one of the most important bases for the cholesterol-lipid-lipoprotein concept of atherogenesis. To appreciate fully the significance of the findings of experimental atherosclerosis, it is necessary to delineate its "prehistory." Prior to 1910, repeated experimental efforts to reproduce the lesion of human atherosclerosis in laboratory animals had met with consistent failure. In 1910-1912 this objective was finally accomplished in rabbits by the feeding of cholesterol. In recent years atherosclerosis has been successfully induced in many laboratory animals, exclusively by procedures effecting an alteration in cholesterol-lipid-lipoprotein metabolism. All these experimental regimens induced a sustained hypercholesteremic hyperlipemia. Clearly, a disturbance in cholesterol-lipid-lipoprotein metabolism is a *sine qua non* for experimental atherogenesis.

The production of experimental atherosclerosis in several species made possible the recent extensive, fruitful research assault in the laboratory, proceeding predominantly along two lines; namely, the influence of dietary and of humorohormonal factors on lipid metabolism and the atherogenic process. Space does not permit even an outline summary of the recent achievements of experimental atherosclerosis. Suffice it to note that animal studies have illuminated the key role of high-cholesterol–high-fat diets in the pathogenesis of atherosclerosis. They

have contributed in clarifying the relationship of dietary imbalance; for example, excess of cholesterol, lipids, and calories and deficiency of other nutrients (e. g., the sulfhydril-containing amino acid methionine), to atherogenesis. They have greatly clarified long-standing problems concerning interrelationships among hypertension, local vascular damage, and atherosclerosis. They have helped in elucidating such key problems as the possible aggravating influences of renal disease, of hypothyroidism, and of exogenous insulin on atherogenesis. Experimental studies have also made a decisive contribution by demonstrating that ovarian estrogen secretion is probably the key factor accounting for the resistance of women before menopause to coronary atherosclerosis.

On several fronts, achievements in the animal laboratory have progressed to the point justifying inauguration of meticulously designed and controlled clinical evaluations of potential new prophylactic and therapeutic procedures for man. Several such long-term studies are now in progress, and more are the order of the day. Inevitably, from the very nature of the disease, such evaluations require several years of assay, since the sole reliable criterion for assessing the efficacy of a given regimen is its effect on the duration of survival.

Obviously, it would be unsound to assert that the recent upsurge in atherosclerosis research and the resultant expansion of knowledge have yielded a solution of the problem. Although much valuable new information has been gained, many things remain unclear and new problems have arisen as old ones were solved. Thus, the revelation of differences in atherogenic response of different arterial beds; e. g., the coronary arteries and the aorta, has posed the important problem of the cause of these differences. The demonstration that considerable morphological coronary atherosclerosis may exist in middle-aged and elderly individuals without development of clinical coronary heart disease has urgently posed the problem of the reasons for this phenomenon. Similarly, experimental and clinical evidence showing interrelationships among diet, plasma lipids, blood clotting, and anticoagulant-clearing factors has necessitated renewed attention to the role and mechanisms of intramural hemorrhage and thrombosis in the pathogenesis of myocardial infarction and ischemic heart disease. The demonstration of species differences in cholesterol-lipid-lipoprotein metabolic response to high-cholesterol–high-fat diets has posed the problem of the basis for and significance of these species differences. These and other new problems posed by recent experiments serve to compel recognition that sooner or later all conclusions from animal research must be reexamined and verified, or modified, by studies in man.

Clearly, significant progress has been made toward our goal, a scientific understanding of the atherosclerosis problem, enabling effective prophylaxis and therapy. Almost certainly, our general theoretical framework of reference, the cholesterol-lipid-lipoprotein concept, is sound. The goal is perhaps in sight, but it has not yet been reached. Like an iceberg, more is hidden than is seen. Considerable hard work still lies ahead—on the part of many, from multiple cooperating disciplines, working in the best traditions of scientific objectivity, perseverance, and enthusiasm.

CHRONIC SUBLUXATING ANKLE

A significant percentage of patients who "sprain" an ankle sustain a permanent disability.[1] In 1942 Hughes [2] wrote that in 57 cases of injury to the ankle without evidence of bony change about half of the patients showed some tilting of the talus when roentgenograms were made with the ankle in forced inversion. Leonard [3] and Pennal [4] assert that tears of the fibular collateral ligament of the ankle severe enough to be demonstrable roentgenologically in forced inversion should be treated in plaster for 6 to 10 weeks. If the injury to the ligaments is extensive, involving a complete tear of the anterior talofibular and calcaneofibular ligaments, it has been proposed that the ligament be repaired primarily.

According to Kelley and Janes,[5] there is extant a group of patients who eventually develop chronic subluxating ankles, most of them sustaining the disability as the result of improper treatment. Excellent results were obtained by these authors at the Mayo Clinic between 1950 and 1954; a small group of patients, ranging in age from 18 to 56 years, underwent the Watson-Jones reconstruction of the fibular collateral ligament of the ankle. The average duration of symptoms among these patients had been seven years. The original injury in each instance had been treated lightly, with the patients subsequently reporting "sprains" of the ankle. Intermittent pain in the ankle associated with swelling below the lateral malleolus was the commonest complaint.

The conservative approach to treatment incorporates use of a wide heel or an outer-heel wedge, together with appropriate exercises of the peroneal muscles. Kelley and Janes state that the best surgical treatment of this condition encompasses reconstruction of the fibular collateral ligament according to the method employed by Watson-Jones. This method utilizes the peroneus brevis tendon, which is severed from its muscular origin and is run through a 0.25-in. drill hole in the fibula, through a drill hole in the talus at the level of the sinus tarsi, and back through a drill hole in the fibula, at which point the tendon is attached to itself. The advantage of the procedure lies in the fact that it restores the important anterior talofibular ligament by means of a tendon that is not likely to stretch. Six of seven patients undergoing the Watson-Jones procedure obtained an ankle that was stable and free of pain and swelling without excessive limitation of motion.

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1. Bonnin, J. G.: Hypermobile Ankle, Proc. Roy. Soc. Med. **37**: 282-286 (April) 1944.

2. Hughes, J. R.: Sprains and Subluxations of Ankle-Joint, Proc. Roy. Soc. Med. **35**: 765-766 (Oct.) 1942.

3. Leonard, M. H.: Injuries of Lateral Ligaments of Ankle: Clinical and Experimental Study, J. Bone & Joint Surg. **31-A**: 373-377 (April) 1949.

4. Pennal, G. F.: Subluxation of Ankle, Canad. M. A. J. **49**: 92-95 (Aug.) 1943.

5. Kelley, J. H., and Janes, J. M.: Chronic Subluxating Ankle, A. M. A. Arch. Surg. **72**: 618-621 (April) 1956.

THE PRESIDENT'S PAGE

A MONTHLY MESSAGE

This will be the last time that I communicate so intimately with you all everywhere in America. It has been a pleasant task to come into your homes and offices once a month for this little intimate chat, and I have appreciated the privilege very much. From your many letters I know that we have been in a close and friendly relationship. I am sorry that this is the last page, and so I would like briefly to talk to you about some things I feel are very important.

We must be alert to find more adequate means for professional care for our people who are in their terminal illness. These patients, even though scientifically you can do nothing for them, need your professional care more than ever before. Never forget, someday you and I are going to need it too. The development of chronic illness and convalescent beds is a necessity in all areas of the country.

The relationship between ourselves and other groups in the community is better today than it has ever been, but this effort on our part must not be neglected. It is our duty to take an active interest in all groups whose main objective is community betterment. As we accomplish this, we must ever remember our duty as citizens. We must align ourselves with the party of our choice and register and vote in every election. They are all important. We must support those candidates who favor our point of view in health matters and be opposed politically to all those candidates who take the point of view that we believe is not in the best interests of the public's health.

Participation in the activities, particularly the business activities, of our county societies is also a must. We must make every attempt to attend the business discussions of our local societies whether we are members of the faculties of our schools or whether we are just members in competitive practice. We need the thinking of all men in medicine. Nonattendance at your medical society meeting means an affirmative vote on all decisions that are made. You have no right to criticize the action of the local, state, or national organization unless you do accept your own responsibility as a member of organized medicine.

A serious part of our obligation and duty as members of the county society is the indoctrination of the young practitioner who has just started to practice in the area. Remember, you are his example. He must be taught by you, by example and precept, that just the scientific application of his newly gained knowledge is not enough to make him a good physician. He must be taught sympathy and kindness and above all that the art of medicine—while neglected—is still necessary if one would have a full and satisfying professional life. By precept and example young dedicated men will be encouraged to study medicine not for the financial reward primarily but for the opportunity to be of service to mankind. If you are not afraid to work, the monetary reward will take care of itself.

I think every physician should recognize that his medical education was subsidized by someone, for none of the tuition fee charged was adequate. There is a loyalty to one's medical school, and there should be a loyalty to medical education as a whole.

I certainly believe THE JOURNAL of the American Medical Association is "must" reading for all of us. Each week there is found in this publication a summation of all our activities, and there is within its pages a gold mine of the best scientific and general information. It will pay large dividends for all of us to keep abreast of current affairs in the field of medicine.

It is also incumbent upon us to give medical facts to the press and public. A good press is a grand ally. There is nothing in the Principles of Medical Ethics to prevent good press relationships. It is time the members of the medical profession ceased hiding medical accomplishment under a bushel. Make friends with the representatives of your local press, and make it your policy to tell them the truth. The public is entitled to know and have the facts concerning medical progress and research.

In closing, if we strive for these things, if we accentuate the spiritual values in medicine as we accept the scientific progress, medicine will continue to lead us forward in the service of humanity, and at the end of the road we will be rewarded by the "well done thou good and faithful servant." *Adios.*

ELMER HESS, M.D., Erie, Pa.

ORGANIZATION SECTION

FEDERAL MEDICAL LEGISLATION

Second Session, 84th Congress

Civilian Aviation Medicine

Congressman Priest (D., Tenn.), after consultation with the Civil Aviation Medical Association, the National Airlines Pilots Association, and several interested individuals, has introduced, in H. R. 10228, a measure that would establish in the Civil Aeronautics Administration an office of civilian aviation medicine and create a medical research laboratory.

Senator Magnuson (D., Wash.), in S. 3677, has introduced an identical measure. The civil air surgeon, under the immediate supervision and direction of the administrator of the Civil Aeronautics Administration, would promulgate regulations regarding standards of fitness for airmen, establish minimum human requirements in aircraft design, and provide for medical examination of civil airmen and issuance of medical certificates to civil airmen. He would have authority to make grants to universities, hospitals, laboratories, and other public or private institutions and to individuals, for research relating to (*a*) causes and prevention of physical and mental conditions of civil airmen that might adversely affect safety in air commerce, (*b*) human requirements in aircraft design, and (*c*) conditions of operation and medical causes of accidents in air commerce. A federal advisory council on civil aviation medicine would be authorized. The bill authorizes $2,500,000 for adequate buildings and facilities for use by the laboratory. It was referred to the Interstate and Foreign Commerce Committee.

Medical Facilities Construction at State Soldiers' Homes

Congressman Kee (D., W. Va.), in H. R. 10268, would provide assistance to states in the construction, modernization, or additions for the improvement of domiciliary or hospital buildings of soldiers' homes operated by a state or territory by a grant to subsidize in part the capital outlay. The bill would authorize 5 million dollars annually for five consecutive years, which would have to be matched dollar per dollar by the state. This bill was referred to the Veterans' Affairs Committee.

Social Security Amendments

Senator Kefauver (D., Tenn.), in S. 3614, would liberalize the public assistance provision of the Social Security Act in four fields:

Old-Age Assistance.—This measure would maintain the present payment by the federal government of $20 of the first $25 that the states pay to recipients of old-age assistance and increase the maximum monthly payment that can be made to an individual to $100. The federal government would participate in the last $75 thereof on a 50-50 basis. In providing assistance, the state agency would disregard the first $50 of earned income, a home worth $5,000 or less, the financial status of the recipient's family, donations of surplus food, and $1,200 of personal property. Women recipients would be eligible at age 62 instead of age 65.

Aid to Dependent Children.—The federal government would contribute four-fifths of the first $15 and one-half of the balance up to $45 for one child and up to $30 in addition for each of the other dependent children in the same home. The state agency would disregard the first $30 of earned income in a household, ownership of a home assessed at less than $5,000, and any donation of surplus food.

Aid to the Blind.—The federal contribution for aid to the blind would be four-fifths of the first $25, plus one-half of additional payments up to a total of $100 per month. The state agency would disregard the first $50 of earned income, ownership of a home assessed at less than $5,000, financial status of the recipient's family, donation of surplus food, and the first $1,200 of all personal property owned by such individual.

Aid to the Permanently and Totally Disabled.—The federal government would contribute four-fifths of the first $25, plus one-half of additional expenditures up to a total of $100 per month. The state agency would disregard the same items listed above under the aid to the blind program. This measure was referred to the Finance Committee.

Atomic Energy for Nonprofit Institutions

Senator Jackson (D., Wash.), in S. 3621, would authorize the Atomic Energy Commission to enter into contracts with universities, colleges, and hospitals to assist financially in construction and operation of reactors and other facilities for training, for research and development, for the generation of usable energy, or for medical therapy. This bill was referred to the Joint Committee on Atomic Energy.

Medical Care for Contract Surgeons

Senator Smathers (D., Fla.), in S. 3634, would authorize hospitalization and medical treatment for persons who had served as acting assistant or contract surgeons or contract dental surgeons, with the War Department or the Department of the Army. The extent of care would be the same as that furnished veterans of any war for non-service-connected disabilities. This bill was referred to the Committee on Labor and Public Welfare.

Child Health and Welfare Amendments

Congressmen Cooper (D., Tenn.) and Reed (R., N. Y.) have introduced identical measures, H. R. 10283 and H. R. 10284, respectively, "to amend and improve

Prepared by the Washington Office of the American Medical Association.

the child welfare provisions of the Social Security Act, to authorize special project grants to institutions of higher education or research in connection with maternal and child health and crippled children's services." This measure would authorize the earmarking of up to 12.5% of the annual appropriation for maternal and child health services for special projects of regional or national significance and for the first time would permit such special project grants to be made not only to the state agencies administering state plans but also to public and nonprofit institutions of higher education or research with the concurrence of the state agency. A like proportion of the appropriations for crippled children's services would be earmarked for similar grants. Both bills were referred to the Ways and Means Committee.

Public Welfare Programs

Congressman Forand (D., R. I.), in H. R. 10302, would amend the Social Security Act to permit states to develop "an optional alternative" to the present programs of public assistance and child welfare services to which the federal government makes a financial contribution. A state could establish a public assistance program based entirely upon need, providing the applicants are not receiving assistance under one of the present categorical public assistance programs. The federal contribution would range from 50% to 80% of the total cost, depending upon the per capita wealth of the state. Assistance could include medical care through payments by the agency administering the plan to persons, agencies, or institutions furnishing or procuring such service. This was referred to the Ways and Means Committee.

Veterans

Veterans Hospitalization.—Congressman McDonough (R., Calif.) proposes, in H. R. 10391, that any combat veteran who applies to the Veterans Administration "for hospitalization for a disease or injury which he claims was incurred or aggravated in combat service immediately would be admitted to the VA facility or hospitalization pending a determination of whether such disease or injury actually was service-connected. Hospitalization furnished by reason of this paragraph shall be furnished without charge therefor."

Combat and Overseas Veterans Hospitalization Priority.—Congressman Kearney (R., N. Y.), in H. R. 10518, would provide that "Veterans, who have engaged in combat or who have served overseas, and who are in need of hospitalization or domiciliary care and are unable to defray the necessary expenses therefor (including transportation to and from the Veterans' Administration facility) shall be given priority in admission for such hospitalization or domiciliary care over all other persons except veterans in need of hospitalization or domiciliary care for service connected disabilities."

VA Outpatient Treatment for Non-Service-Connected Disabilities.—Congressman Rogers (R., Mass.), in H. R. 10842, would authorize outpatient care for non-service-connected disabilities for veterans entitled to receive a pension for 100% permanent and total non-service-connected disability. At the present, outpatient care is authorized only for veterans with service-connected disabilities and for veterans of the Spanish American War, the Boxer Rebellion, and the Philippine Insurrection. The proposed measure would make eligible for outpatient care approximately 500,000 veterans from World War I, 58,000 from World War II, and 2,000 from the Korean War. All of the above bills were referred to the Veterans' Affairs Committee.

EXHIBITION OF RUSSIAN-MADE FILMS AT ANNUAL MEETING

A special exhibition of films produced by the Academy of Medical Science of the U. S. S. R. will be held Monday night, June 11, in the Grand Ballroom of the Sheraton Hotel at 8 p. m. These films are a part of an official governmental exchange program and have been made available to the American Medical Association for presentation at the Annual Meeting. The titles of these pictures, produced in 35 mm. color, are as follows: (1) Anastomosis of the Aorta and the Pulmonary Artery in Congenital Heart Disease, (2) Local Anesthesia in Surgical Treatment of Mitral Stenosis, and (3) Segmental Resection of the Lung in Tuberculosis. The films will be introduced and discussed by Dr. Willis J. Potts and Dr. Jerome Head of Chicago.

DR. LEVEROOS TO LEAVE COUNCIL ON MEDICAL EDUCATION AND HOSPITALS

Dr. Edward H. Leveroos, Director, Division of Hospitals and Graduate Education of the Council on Medical Education and Hospitals, will leave the American Medical Association staff on July 1 to become Director of the Ochsner Foundation Hospital in New Orleans. During his period with the American Medical Association, Dr. Leveroos was responsible for the planning, organization, and direction of the activities of the graduate education section of the Council, including the program of approval of hospitals for intern and residency training. He has played an important role in correlating the activities of the Council in the field of residency training in the specialties with those of the American boards concerned. He also maintained liaison with the American boards and with the appropriate sections of the Armed Services, Veterans Administration, the United States Public Health Service, and various civilian agencies engaged in graduate medical education. His duties included the preparation of the Annual Report on Internships and Residencies and the lists of hospitals approved for graduate training published annually in THE JOURNAL.

The Council on Medical Education and Hospitals wishes to acknowledge with appreciation the constructive contributions Dr. Leveroos has made to its program and to the over-all field of graduate medical education.

MEDICINE AND THE LAW

The Judicial Council has authorized the publication of the following opinions. These opinions, and others approved by the Judicial Council, will be published in Medicine and the Law. These opinions will eventually be compiled and published separately as annotations to the Principles of Medical Ethics.

Question: Am I ethically obligated to give a patient a copy of my records?

Answer: The Judicial Council does not believe that Chapter II, Section 3 intends or requires that a physician give a copy of his records to his patient. These records are primarily the physician's own notes compiled during the course of diagnosis and treatment so that he may review and study the course of the illness and his treatment. The records are medical and technical, personal and often informal. Standing alone they are meaningless to the patient but of value to the physician and perhaps to a succeeding physician. The patient, however, or one responsible for him, is entitled to know the nature of the illness and the general course or regimen of therapy employed by his physician. The extent to which the physician must advise his patient may be limited by the nature of the illness and the character of the patient. The physician in advising his patient must always act as he would wish to be treated were he in a like situation.

Question: A colleague has asked me to send him my records concerning a former patient of mine who presently is under his care. Am I obligated to send him these records?

Answer: The interest of the patient is paramount in the practice of medicine, and everything that can reasonably and lawfully be done to serve that interest must be done by all physicians who have served or are serving the patient. When a colleague who is presently treating a patient requests records from another physician who has formerly treated the patient, that former physician should promptly make his records available to the attending physician.

No set rule can be laid down to cover the manner in which the records are to be transmitted to the attending physician. Under some conditions a personal inspection of the records might suffice; under others an oral report of what is contained in the records would be of help; or in other circumstances a summary of the records might be made. In extreme cases, a physician might lend his complete record to the attending physician. The manner of making the report—or the information contained therein—available to the succeeding physician is immaterial and will depend on the circumstances of each case. Certainly, however, the attending physician should not demand or expect more information from the former physician than is necessary to give the patient adequate care in the present illness.

The Judicial Council assumes, of course, that proper authorization for the use of these records has been granted by the patient.

Question: Is the listing of one's name in a commercially sponsored advertising directory in keeping with the Principles?

Answer: No. The Principles proscribe the solicitation of patients directly or indirectly. The House of Delegates of the Association has expressed disfavor with the practice of permitting one's name to be listed in a commercial advertising directory because it is or may be interpreted to be the indirect solicitation of patients. In 1936, a resolution was introduced in the House of Delegates. It reads as follows: "Whereas, certain commercial interests are publishing medical directories, listing physicians by specialty and otherwise, as available for insurance and compensation work, and other professional services, and whereas, participation by listing in these lay publications merely serves for the profit of the promoters and is furthermore more technically indirect solicitation of patients, be it Resolved that the Arkansas Medical Society condemns these practices as unethical and forbids its members to continue listing their names in such directories and be it further resolved that the Arkansas Medical Society requests the House of Delegates of the American Medical Association to take similar action." The Reference Committee to which this resolution was presented reported that it "is of the opinion that most, if not all, of the directories described in the resolutions condemning as unethical the listing of physicians by specialty in directories published by commercial concerns, which were introduced by Dr. Brooksher of Arkansas, are but subtle ways of avoiding the pronouncement of the Principles of Medical Ethics concerning solicitation of patients, under a guise of buying a directory when the real intent is the purchase of the publication of the buyer's name in the directory for the purpose of obtaining patients." The reference committee report recommending approval of the resolutions was adopted by the House of Delegates.

The Judicial Council quotes this action for emphasis and calls attention to the fact that the action of the House of Delegates is binding on the members of the Association. The Council would further state that a physician who uses or permits the use of his name in a commercial directory that fails to include on like terms and without discrimination the names of all licensed physicians practicing in the area served by the directory has the burden of proving that his action is in keeping with the Principles.

MEDICAL NEWS

CALIFORNIA

Course on Cardiovascular Diseases.—The University of Southern California School of Medicine, Los Angeles, will offer a course on Diagnosis and Management of Cardiovascular Diseases, July 20-22 (tuition fee, $65). Short lectures and panel discussions will be given each morning at the Hotel Statler. During the afternoons the physicians will meet at the Good Hope Clinic for the examination and study of cardiac patients. Registration for this course closes July 10. For information contact Dr. Phil R. Manning, Director, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Ave., Los Angeles 33.

Quarantine on Mussels.—The yearly quarantine of mussels for human consumption, recently established along the entire California coast, including San Francisco Bay, will be in effect to Oct. 31, according to Dr. Malcolm H. Merrill, San Francisco, state health director. Mussels may be used for bait during the ban but must be broken open and placed in containers plainly marked in large print "For fish bait only. Unfit for human consumption." Clams should be cleaned and washed thoroughly before cooking, and all dark parts, where the poison concentrates during the May-October period, should be discarded. Only the white meat should be eaten. In addition, clams should be taken from areas free from sewage contamination.

IDAHO

State Medical Meeting at Sun Valley.—The 64th annual meeting of the Idaho State Medical Association will be held at Sun Valley, June 17-20, under the presidency of Dr. Robert S. McKean, Boise. Dr. John L. Parks, professor, department of obstetrics and gynecology, George Washington University School of Medicine, Washington, D. C., will discuss "X-Ray Diagnosis in Pregnancy," "Feminology After Fifty," "The Management of Ovarian Tumors," and "Urinary Incontinence in the Female." Dr. Edgar van N. Allen, professor of internal medicine, University of Minnesota Graduate School, Minneapolis-Rochester, will consider "The Use of Anticoagulants," "The Treatment of Hypertension" (two papers), and "Aneurysms and Occlusion of the Abdominal Aorta." Dr. Walter C. MacKenzie, professor of surgery, University of Alberta Faculty of Medicine, Edmonton, Canada, will speak on "Complications of Biliary Calculi," "Acute Intestinal Obstruction," "Recurrence of Inguinal Hernia," and "The Modern Treatment of Varicose Veins." Dr. L. Henry Garland, clinical professor of radiology, Stanford University School of Medicine, San Francisco, will discuss "X-Ray Diagnosis of Certain Pelvic Disorders," "The Treatment of Carcinoma of the Thyroid," "The Treatment of Carcinoma of the Breast," and "The Place of X-Ray in the Differential Diagnosis of Arthritis." Dr. Frank B. Queen, professor of pathology, University of Oregon Medical School, Portland, will present "Pathologic Physiology of Jaundice," "Nodules of Thyroid and Thyroid Cancer," "Hyaline Membrane Disease, a Common Cause of Death of Premature and Caesarean Section Infants," and "Clinical Implications of Some Recent Studies of Metastases." The program was arranged by Dr. Warren B. Ross, Nampa.

ILLINOIS

Clinics for Crippled Children.—The University of Illinois division of services for crippled children has scheduled the following clinics to which any private physician may refer or bring children for consultative services:

June 20, Chicago Heights (general), St. James Hospital; Salem, Masonic Temple.
June 21, Rockford, St. Anthony Hospital.
June 22, Chicago Heights (cardiac), St. James Hospital.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

Personal.—Dr. Bruce A. Harrison, Colchester, was recently honored at a surprise banquet for his 45 years of service to the community. Dr. Harold M. Camp, Monmouth, secretary of the Illinois State Medical Society for 32 years, was master of ceremonies. The speakers included Dr. F. Lee Stone, Chicago, then president-elect, Illinois State Medical Society, Dr. Joseph T. O'Neill, Ottawa, chairman of its council, and Dr. Charles P. Blair, Monmouth, councilor for the fourth councilor district.

Chicago

Lecture on Growth of Medicine.—In its series of lectures on the growth of medicine (Wednesdays, 5-6 p. m., in Thorne Hall), Northwestern University Medical School on June 6 presented Dr. Morris Fishbein, Chicago, whose subject was "Birth and Growth of the American Medical Association."

Garden for the Blind.—The Chicago Lighthouse for the Blind recently announced that its new headquarters building will have a special garden for the blind, in which tags marked in braille will be attached to the flowers and shrubs. The garden, located in the west side medical center, is a gift of the Chicago Horticultural Society and Garden Center.

Annual Meeting of Gynecologists.—The Chicago Gynecological Society will hold its 75th annual meeting at the Knickerbocker Hotel (Walton Place, just east of Michigan Avenue), June 15 (telephone: WHitehall 3-2000). Dinner (informal), 7:30 p. m., will be preceded by cocktails at 6:30 p. m. and followed by the program at 8:30 p. m. Nonmembers of the society interested in gynecology and obstetrics are invited to attend. Reservations must be made in advance. After dinner "Insurance for Survival" will be considered by William H. Arnold, commanding general, Fifth Army, Chicago. There will be no clinical meeting.

MONTANA

Medicosurgical Conference.—On June 16 the Western Montana Medical Society will sponsor its first Medical-Surgical Conference at the Missoula Hotel in Missoula. The speakers will include Drs. Henry N. Harkins, professor of surgery, and K. Alvin Merendino, associate professor of surgery, University of Washington School of Medicine, Seattle. All Montana physicians are cordially invited.

NEW JERSEY

State Medical Election.—Newly elected officers of the Medical Society of New Jersey include Dr. Lewis C. Fritts, Somerville, president; Dr. Albert B. Kump, Bridgeton, president-elect; Dr. Kenneth E. Gardner, Bloomfield, first vice-president; Dr. F. Clyde Bowers, Mendham, second vice-president; Dr. Marcus H. Greifinger, Newark, secretary; and Dr. Jesse McCall, Newton, treasurer.

NEW YORK

State Medical Election.—The Medical Society of the State of New York recently elected Dr. James Greenough, Oneonta, president; Dr. Thurman B. Givan, Brooklyn, president-elect; and Dr. Thomas M. Watkins, Potsdam, vice-president; and reelected Dr. Walter P. Anderton, New York, secretary; Dr. Ezra A. Wolff, Forest Hills, assistant secretary; Dr. Maurice J. Dattelbaum, Brooklyn, treasurer; and Dr. Samuel Z. Freedman, New York, assistant treasurer.

Doctors' Orchestra.—The New York Doctors' Orchestral Society, of which Dr. Alfred E. Mamelok, New York City, is president, gave a concert April 15 at the New York University School of Education Auditorium. Miss Helen Kenalwasser, violinist, and Mr. Louis Bernsohn, cellist, were the soloists in

Brahms' Concerto for Violin and Cello. The orchestra performed Dvorak's Carnival Overture and New World Symphony. Physicians, dentists, and others engaged in allied professions are invited to become members of the orchestra. Rehearsals are held Thursdays at 8:30 p. m. in the auditorium of P. S. 33, 9th Avenue and 26th Street, Manhattan. For details, call Dr. Benjamin A. Rosenberg, Brooklyn, at NEvins 8-2370.

New York City

Pediatric Orthopedic Service.—A children's orthopedic consultation service was recently opened at Mount Sinai Hospital as a joint venture of the hospital and the city health department. Private physicians, school health doctors, child health stations, and clinics from any borough may refer children to the service, which is in the outpatient building of the hospital, Madison Avenue and 100th Street.

Personal.—At the centennial dinner of the Massachusetts Memorial Hospital, Boston, at which he was the principal speaker, Dr. Howard Rusk was presented with a gold centennial medal.——Dr. Frederick S. Reiss, associate clinical professor of dermatology, New York University Post-Graduate Medical School, gave a lecture Jan. 6 at the Veterans Administration Hospital, Kingsbridge Road, Bronx, on "The Diagnostic Importance of Systemic Fungus Infection."——Dr. Lawson G. Lowrey, assistant professor of psychiatry, Columbia University College of Physicians and Surgeons, discussed "Aspects of Psychotherapy for Both Hospitalized and Office Patients" before the members of the hospital staff of the Veterans Administration Hospital at Northport, L. I., Feb. 2.——Dr. Edwin J. Foley, head of the medical department of Winthrop Laboratories, has been appointed vice-president of the firm. Dr. Foley joined the company in 1933. During World War II he served in the Army Medical Corps in North Africa and Italy.

TENNESSEE

Oak Ridge Institutes for Science Teachers.—A training division of the Oak Ridge Institute of Nuclear Studies will conduct an institute for secondary school teachers June 11-July 6 and another for college and university teachers July 9-Aug. 3. These institutes, which will be sponsored by the National Science Foundation, will include discussions on science experiments, science-teaching methods, and radioisotope techniques.

WEST VIRGINIA

Narcotic Violation.—Dr. Emmett W. Horton, Bluefield, was convicted of a violation of the federal narcotic law and on April 2 was sentenced to a term of two years on nine counts to run concurrently and was fined $2,000 on each count. The sentence was suspended, and he was placed on three years' probation. The defendant was ordered to pay a total fine of $18,000 and to discontinue the practice of medicine.

Annual Postgraduate Session.—The seventh annual postgraduate session of the Barbour-Randolph-Tucker Medical Society (Dr. Donald R. Roberts, president) will be held at the Tygart Valley Country Club, near Elkins, June 21. Dr. Vernon E. Duckwall, Elkins, will moderate the following program at the afternoon session:

- Pre and Postoperative Medical Management of the Surgical Child, Frederic G. Burke, professor of pediatrics, Georgetown University School of Medicine, Washington, D. C.
- Ear Problems, G. Douglas Hayden, associate professor of otolaryngology, Medical College of Virginia, Richmond.
- Clinical Features of Aortic Insufficiency, W. Proctor Harvey, associate professor of medicine, Georgetown University School of Medicine, Washington, D. C.
- Endocrinological Aspects of Disorders of the Blood, Leandro M. Tocantins, professor of clinical and experimental medicine, Jefferson Medical College of Philadelphia.

The Kloman Instrument Company, Charleston, and McLain Surgical Supply, Inc., Wheeling, will be hosts at a social hour, 5 p. m. Dr. William B. Rossman, Charleston, guest speaker at the banquet, will present "Portrait of a Broadway Psychiatrist." The golf tournament will begin at 9 a. m. and end at 2 p. m. A tea for the wives of doctors will be held at 2:30 p. m. at the residence of Mrs. Raymond W. Sass.

GENERAL

Hospital Alumni Association.—The organizational meeting of the Grant Hospital (Chicago) Intern and Resident Alumni Association will be held at the Sherman Hotel, Chicago, June 13, 6:30 p. m. Reservations may be made with Dr. Walter J. Reich, Grant Hospital, DI 8-6400 or CE 6-3040.

Conference on Industrial Research.—A conference on the management of industrial research will be held at the Harriman (N. Y.) campus, June 11-15, under the auspices of Columbia University, New York. Dr. Melvin W. Thorner, professor of psychiatry, University of Pennsylvania School of Medicine, Philadelphia, will participate in a panel on human relations in industrial research, Wednesday morning.

Wanted—Bones and Brains.—Temporal bones and brains and, if possible, the brains from totally deaf children or adults who had had adequate antemortem hearing tests and histories are wanted by the committee on conservation of hearing of the American Academy of Ophthalmology and Otolaryngology. For details on methods of removing the specimens and of shipping them to one of several processing laboratories, phone, wire, or write to Dr. Harold F. Schuknecht, Henry Ford Hospital, Detroit.

Meeting on Vascular Surgery.—The Society for Vascular Surgery will hold its 10th annual meeting at the Conrad Hilton Hotel, Chicago, June 10. The presidential address, "The First 10 Years of the Society for Vascular Surgery," by Dr. George D. Lilly, Miami, Fla., will precede the luncheon, which will be followed by the John Homans Memorial Lecture, "Venous Thrombosis and the Post-Thrombotic Syndrome," by Dr. René Fontaine, professor of surgery and dean of the Faculty of Medicine, University of Strasbourg in France. The program, which includes 24 other speakers by invitation, is open to the medical profession.

International Meeting of Hematologists.—The sixth congress of the International Society of Hematology will convene at the Somerset Hotel, Boston, Aug. 26-Sept. 1 (THE JOURNAL, Nov. 26, 1955, page 1314). A large number of physicians from western Europe, Latin America, and the Orient will attend, as will seven Russian hematologists and several from Czechoslovakia, Poland, and Hungary. The first day will be devoted to leukemia and the second to nucleonics, with a panel discussion moderated by Dr. Eugene P. Cronkite of Brookhaven National Laboratory, Upton, N. Y. Interlingua, one of the four official languages, is to be used for all the written translations and documents.

American College of Angiology.—The second annual meeting of the American College of Angiology will convene at the Drake Hotel, Chicago, June 9-10. Dr. Leo Loewe, New York, will deliver the presidential address at 11:20 a. m. Saturday. "Experiences with Anticoagulant Therapy" by Dr. Joseph H. Nicholson, Lawrence, Mass., will be the first of 28 scientific papers to be presented. "Observations on the Occurrence of Clubbed Fingers" by Dr. S. Epstein, New York, the concluding presentation, will be read Sunday at 4 p. m. Cocktails at 6 p. m. will precede the annual banquet, 7 p. m., at which Paul De Kruif, Ph.D., Holland, Mich., roving editor for *Reader's Digest,* will be the speaker.

Israel Medical Association.—The American Physicians Fellowship Committee, Inc., of the Israel Medical Association, announces that the annual assembly and banquet will be held at the Morrison Hotel in Chicago, June 11, during the A. M. A. convention. A cocktail party, 5:30-8 p. m., will precede the dinner. The guest of honor will be Dr. Moshe Sherman, president of the Israel Medical Association, and the main speaker will be Dr. George J. Mohr, Chicago, who will discuss "Medical Perspectives in Israel—Personal Observations." A musical program will follow. Reservations may be made by writing to the American Physicians Fellowship Committee of the Israel Medical Association, 1330 Beacon St., Brookline 46, Mass.

Directory of Clinical Chemists.—The American Board of Clinical Chemistry, Inc., which has certified 246 clinical chemists, has issued a complete Directory of Certified Clinical Chemists that is available without charge to hospital departments or other

laboratories engaging in clinical chemistry. Until July 1 this may be obtained from Dr. Oliver H. Gaebler, Henry Ford Hospital, Detroit 2; thereafter correspondence should be addressed to the secretary-treasurer, William A. Wolff, Ph.D., Bowman Gray School of Medicine, Winston-Salem 7, N. C. Clinical chemists interested in being certified may write for the instructions to applicants for certification. The next regional examinations will probably be held next October.

Commemorative Stamp.—A special 3-cent stamp commemorating the 50th anniversary of the passage of the Pure Food and Drug Law will be first placed on sale at Washington, D. C., June 27. The stamp (0.84 by 1.44 in.) will be issued in sheets of 50. The central design was reproduced from a photograph of the late Harvey W. Wiley, "father" of the pure food and drug acts. Stamp collectors desiring first-day cancellations of this issue may send a reasonable number of addressed envelopes to the Postmaster at Washington 13, D. C., with money order remittance to cover the cost of the stamps to be affixed. To expedite the handling of covers, the outside envelope to the postmaster should be endorsed "First-Day Covers."

Meeting of Electroencephalographers.—The 10th annual meeting of the American Electroencephalographic Society will convene at the Claridge Hotel, Atlantic City, N. J., June 15-17, preceding the annual meeting of the American Neurological Association. The presidential address, "New Dimensions in Electroencephalography," will be presented by Dr. Reginald G. Bickford, Rochester, Minn., Saturday, 11:20 a. m. The program includes a colloquium on "The History of Neurophysiology" Friday evening under the chairmanship of Dr. Alexander Forbes, Boston, and a symposium on "EEG in the Diagnosis of Coma States" Sunday morning under the chairmanship of Dr. Jerome K. Merlis, Boston. The annual banquet will take place Saturday, 7:30 p. m.

Physicians Art Exhibit.—The American Physicians Art Association will hold its annual meeting June 11-15 at Navy Pier in Chicago, where its exhibit will be presented under the sponsorship of Sharp & Dohme. The famous Artists School of Westport, Conn., will donate the services of Mr. Dong Kingman, Brooklyn, and Mr. Fletcher Martin, Woodstock, N. Y., to help in the judging and to give lectures and demonstrations at the evening meetings, which will be held Monday, Tuesday, and Wednesday (award night), 8 p. m., at the Drake Hotel. Mr. Kingman, twice winner of the Guggenheim Fellowship, has taught at Columbia University and at Hunter College. Mr. Martin, holder of the Van Rensselaer Wilbur Prize, has served as artist-in-residence at the University of Iowa and as head of the painting department of the Kansas City Art Institute.

Conference of State Medical Presidents.—The 12th annual meeting of the Conference of Presidents and Other Officers of State Medical Associations will convene at the Palmer House, Chicago, June 10, 2 p. m., under the presidency of Dr. Charles L. Farrell, Pawtucket, R. I. The session will open with presentation of "The Medical Practitioner—Yesterday, Today, Tomorrow" by Dr. Guthrie Y. Graves, Bowling Green, Ky., president-elect of the conference. "Workers in Wheelchairs" will be discussed by Mr. Henry Viscardi Jr., president, Abilities, Inc., West Hempstead, N. Y., and "The Body Politic" by Howard Pyle (formerly governor of Arizona), Administrative Assistant to the President, Washington, D. C. The program will close with "The Healer Goes Forth" by Allen A. Stockdale, D.D., LL.D., National Association of Manufacturers, New York.

Meeting of Gastroscopic Society.—The annual meeting of the American Gastroscopic Society will convene at the Hotel Knickerbocker, Chicago, June 10-11. The sessions will open Sunday, 10 a. m., with the president's address by Dr. Donovan C. Browne, New Orleans, which will be followed by a film, "Multiple Position Technic for Gastroscopy," by Dr. Leonidas H. Berry, Chicago. A film, "Esophagoscopic Views of Lesions of the Esophagus," will be exhibited at 11 a. m. by Dr. Paul H. Holinger and Dr. Kenneth C. Johnston, Chicago. At 2:10 p. m. "Review of Gastroscopic Technics and Experiences in England" will be presented by Dr. Percy E. Thompson Hancock, London. The session will end with "Gastroscopic Biopsy with Tomenius Biopsy Gastroscope" by Dr. John H. Tomenius, Stockholm, Sweden. Cocktails and the annual banquet are scheduled for 6:30 p. m. A clinical session will be held Monday, 9 a. m., at the Cook County Hospital.

Meeting on Investigative Dermatology.—The 17th annual meeting of the Society for Investigative Dermatology will be at the Hotel Sherman, Chicago, June 9-10. The presidential address, "Dermatologic Research: An Office Procedure?" by Dr. J. Lamar Callaway, Durham, N. C., will open the scientific sessions Saturday. The afternoon session will begin at 2 p. m. with "An Improved Technique for Capillary Microscopy of the Skin" by Major Michael J. Davis, M. C., and Capt. Allan L. Lorincz, M. C., Walter Reed Army Institute of Research, Walter Reed Army Medical Center. The cocktail party and dinner will be at 7 p. m. The Sunday session will open at 9 a. m. with "The Effect of Gelatin and Collagenous Tissue on Dermatophyte Growth" by Capt. Paul H. Jacobs, M. C., U. S. A. F., and Captain Lorincz. The closing address, "Excretion of Creatine and Creatinine in the Urine of Patients with Dermatomyositis," will be presented Sunday afternoon by Dr. Herbert B. Christianson, Dr. Paul A. O'Leary, and Marschelle H. Power, Ph.D., Rochester, Minn.

Ames Award Contest.—The American College of Gastroenterology in cooperation with the Ames Company of Elkhart, Ind., announces the 1956 Ames Award Contest for the best papers in gastroenterology by fellows in gastroenterology, residents, or first or second year interns. In addition to the first prize of $500 and the second prize of $250, the winners will receive a certificate of merit, and a one-year subscription to the *American Journal of Gastroenterology*, official publication of the college. For the best paper published in that journal during the 12 months ending June 30, 1956, for which no prize has been previously awarded, $250 will be given. All papers submitted must represent original work, must not have been previously published except for abstracts or short preliminary reports, and must not have been previously presented at any national meetings. All entries for the 1956 prizes must be typewritten in English, double-spaced on one side of the paper, and submitted in six copies. Entries must be received no later than July 15, 1956, and should be addressed to the Research Committee, American College of Gastroenterology, 33 W. 60th St., New York 23.

Medical Seminar Cruise.—Dr. Wilburt C. Davison, dean, and Dr. William McNeal Nicholson, professor of medicine and director of postgraduate education, Duke University School of Medicine, Durham, N. C., announce an 18-day Postgraduate Medical Seminar cruise, sailing from New York, Oct. 27, aboard the 24,000-ton, air-conditioned S. S. Nassau with stops at Madeira, Casablanca, Cadiz, Palermo, Naples, and Rome. Extensions may be made for visiting other European points of interest. There will be no registration fee. Cost of attending the medical cruise may be deducted when computing federal income taxes. There will be 25 hours of formal teaching. The faculty will include Drs. Davison, Nicholson, Lenox D. Baker, professor of orthopedic surgery, Leslie B. Hohman, professor of psychiatry, and Edward S. Orgain, professor of medicine. Although the seminar cruise will be sponsored by the school, it will be open to qualified physicians anywhere. Bookings may be made not only by physicians and members of their families but by any who desire to make the cruise. The cruise will be conducted by the Allen Travel Service, Inc., 550 Fifth Ave., New York 36, through which reservations can be made.

Meeting of Diabetes Association.—The American Diabetes Association will hold its 16th annual meeting June 9-10 at the Drake Hotel, Chicago, under the presidency of Dr. Henry T. Ricketts, Chicago. The Banting Memorial Lecture, "Recent Advances in Insulin Research," will be presented Saturday, 10:30 a. m., by Dr. William C. Stadie, professor of research medicine, University of Pennsylvania School of Medicine, Philadelphia. The Banting medal will be presented to Dr. Stadie after the presidential address at the banquet, Saturday, 7:30 p. m. Presentation of the Banting medal to Dr. Louis H. Newburgh, Valley Center, Calif., professor emeritus, University of Michigan Medical School, Ann Arbor, will also be made at the

banquet, as will presentation of a citation to Mrs. Earl R. Hoover, vice-president, the Diabetes Association of Greater Cleveland. An address, "Social Homeostasis," will be delivered by Alfred E. Emerson, Ph.D., professor of zoology, University of Chicago. A panel discussion on unstable diabetes is scheduled for Sunday, 11:10 a. m., with Dr. Alexander Marble, Boston, as moderator. On Sunday at 2:30 p. m. an invitational address, "On the Mechanism of the Effect of Muscular Work on the Hyperglycemia of Diabetes," by Dr. Rachmiel Levine, Dr. Maurice S. Goldstein, and Irving B. Fritz, Ph.D., Chicago, will precede a panel discussion on vascular disease (Dr. Arthur R. Colwell, Chicago, moderator). Dr. Philip M. LeCompte, Boston, will participate by invitation on the panel. Many other speakers have been invited to be on the program.

Society News.—The Canadian and United States Section, **International College of Surgeons,** which will hold the 21st annual congress at the Palmer House, Chicago, Sept. 12, announces a change in its original plans (THE JOURNAL, May 5, page 82). The speaker will be replaced by the introduction of foreign guests. The following countries will be represented: Argentina, Austria, Bolivia, Brazil, Colombia, Finland, France, Germany, Iraq, Japan, Mexico, Netherlands, Philippines, Southern Rhodesia, Switzerland, Thailand, Turkey, and Venezuela. Reservation requests for the banquet and reception ($15 each) should be accompanied by a check payable to Dr. Chester W. Trowbridge, banquet chairman (715 Lake St., Oak Park, Ill.).——Newly elected officers of the **American Psychosomatic Society** include: Dr. I. Arthur Mirsky, Pittsburgh, president; Dr. Theodore Lidz, New Haven, Conn., president-elect; and Dr. Morton F. Reiser, Washington, D. C., secretary-treasurer. The next annual meeting of the society will be held at Chalfonte-Haddon Hall, Atlantic City, N. J., May 4-5, 1957.——The **Southern Neurological Society** recently elected Dr. W. Gayle Crutchfield, Charlottesville, Va., president; Dr. William F. Meacham, Nashville, Tenn., vice-president; and Dr. C. Douglas Hawkes, Memphis, Tenn., secretary-treasurer.——Officers of the **Association of American Physicians and Surgeons** include: Dr. Charles W. Pavey, Columbus, Ohio, president; Dr. Cyrus W. Anderson, Denver, president-elect; Dr. William L. Baughn, Anderson, Ind., secretary; and Dr. Andrew J. Sullivan, Chicago, treasurer.

Foreign Lecturers in Biochemistry.—The International Congress of Clinical Chemistry, which will meet at the Hotel Barbizon-Plaza, New York, Sept. 9-14, announces the availability of the following European speakers for lectures in biochemistry:

T. H. J. Huisman, department of pediatrics, University of Groningen, The Netherlands, Pathology of Hemoglobin.
B. Josephson, St. Eriks Hospital, Stockholm: Fluid Compartments and Electrolyte Metabolism.
E. J. King, Postgraduate Medical School of London: Enzymes in Pathological Chemistry; also: Chemistry of Silicosis.
N. F. Maclagan, department of chemical pathology, University of London: Mucoproteins.
R. Ma Garia, department of physiology, University of Milan: Blood Electrolytes.
J. Nordmann, Salpetriere, Paris: Citric Acid Cycle in Clinical Chemistry.
M. Sanz, Hopital Cantonal, Geneva: Instrumentation and Standardization of Ultramicromethods.
N. Siliprandi, Institute of Biological Chemistry, University of Rome: Vitamins of the B-Complex in Human Pathology.
Z. Stary, Institute of Biochemistry, University of Istanbul: Mucoproteins.
C. P. Stewart, Royal Infirmary, Edinburgh: Blood Electrolytes.
J. C. M. Verschure, University of Utrecht: Lipoproteins; also: Chromatography of Bile.
Ian D. P. Wootton, Postgraduate Medical School of London: Standardization in Clinical Chemistry.
Ferd. Wuhrmann, Kantonsspital, Winterthur, Switzerland: Electrophoresis of Serum Proteins.

Information may be obtained from the chairman of the scientific program committee, Harry Sobotka, Ph.D., Mount Sinai Hospital, New York 29.

LATIN AMERICA

Schweitzer Hospital in Haiti.—The Albert Schweitzer Hospital, Deschapelles, Haiti, is nearing completion and will soon begin receiving patients. The $1,500,000 hospital is the project of Dr. and Mrs. William L. Mellon, who made a trip to Lambarene in French Equatorial Africa after World War II, before they themselves became affiliated with medicine. In 1949 they went to New York to interview Dr. Schweitzer during his visit there and shortly afterward enrolled in the Tulane University of Louisiana School of Medicine, New Orleans, where Mr. Mellon received his medical degree in June, 1953. The hospital will be staffed by Dr. Mellon and four other physicians from the United States. The nursing staff will be headed by Mrs. Mellon and four Haitian nurses who have spent two years studying in North American hospitals.

FOREIGN

Pediatric Course on Mental Deficiency.—A course on problems raised by mentally deficient children will be offered at the International Children's Centre in Paris, France, from Sept. 17 to Oct. 28. The course, which addresses itself to psychiatrists, psychologists, educators, judges of children's courts, and specialized welfare workers, will place special emphasis on practical work and study circles. Information may be obtained from the Public Relations Service, International Children's Centre, Chateau de Longchamp, Bois de Boulogne, Paris-XVIe; cable address: Centrenfance.

EXAMINATIONS AND LICENSURE

EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY: *Written.* Various locations in the United States and Canada, July 20. Final date for filing application was Jan. 20. Sec., Dr. C. B. Hickcox, 80 Seymour St., Hartford 15, Conn.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY. *Written.* Various centers, July 26. *Oral.* St. Louis, Oct. 12-15. Final date for filing applications was April 1. Sec., Dr. B. M. Kesten, One Haven Ave., New York 32.

AMERICAN BOARD OF INTERNAL MEDICINE: *Written.* Oct. 15, 1956. Final date for filing application was May 1. *Oral Examinations in 1956.* Chicago, June 7-9. Final date for filing application for these three oral examinations was Jan. 3. New York City, Sept. 21-25. Final date for filing application was April 1. *Cardiovascular Disease.* Chicago, June 6. The number of candidates is limited to 24 and the final date for filing applications was Apr. 2. Exec. Sec., Dr. William A. Werrell, 1 West Main St., Madison 3, Wis.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: *Part I.* 1957. Applications now being accepted. Final date for filing applications is Oct. 1. Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

AMERICAN BOARD OF OPHTHALMOLOGY: *Practical Examination.* San Francisco, June 18-21, St. Louis, Oct. 20-24. *Written.* Jan. 21, 1957. Applications must be filed before July 1, 1956. Sec., Dr. Merrill J. King, Box 236, Cape Cottage Branch, Portland 9, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: *Oral. Part II.* Chicago, January 1957. Final date for filing application is Aug. 15. Sec., Dr. Sam W. Banks, 116 South Michigan Ave., Chicago 3.

AMERICAN BOARD OF PATHOLOGY: *Written for Pathological Anatomy and Clinical Pathology,* Oct. 4-6. Final date for filing application is Sept. 1. Sec., Dr. Edward B. Smith, 1040-1232 W. Michigan St., Indianapolis 7.

AMERICAN BOARD OF PEDIATRICS: *Oral, Part II.* Cincinnati, June 8-10; New York City, Oct. 12-14, and San Francisco, Dec. 7-9. Sec., Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PHYSICAL MEDICINE AND REHABILITATION. *Parts I and II.* Chicago, June 16-17. Sec., Dr. Earl C. Elkins, 200 First St., S. W., Rochester, Minn.

AMERICAN BOARD OF PREVENTIVE MEDICINE; *Oral and Written. Public Health.* Philadelphia, Nov. 8-10. Sec., Dr. Ernest L. Stebbins, 615 N. Wolfe St., Baltimore, Md.

AMERICAN BOARD OF PROCTOLOGY: *Oral and Written.* Philadelphia, Sept. 29. Filing date for filing application is June 28. Sec., Dr. Stuart T. Ross, 520 Franklin Ave., Garden City, N. Y.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: *Oral.* New York, Dec. 10-11 and New Orleans, Mar. 18-19. Sec., Dr. David A. Boyd, Jr., 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: Chicago, June 5-9. Final date for filing applications was Jan. 1.; Los Angeles, Sept. 30-Oct. 4. Final date for filing application was June 1. Sec., Dr. B. R. Kirklin, Kahler Hotel Bldg., Rochester, Minn.

AMERICAN BOARD OF UROLOGY: February 1957. Sec., Dr. William Niles Wishard, 1711 N. Capitol Ave., Indianapolis 7.

BOARD OF THORACIC SURGERY. *Written.* Various centers throughout the country, September. Final date for filing application is July 1. Sec., Dr. William M. Tuttle, 1151 Taylor Ave., Detroit 2.

GOVERNMENT SERVICES

ARMY

Training in Thoracic Surgery.—Training in thoracic surgery for Regular Army Medical Corps general surgeons will be offered in an on-the-job, six-month course, beginning July 1. The course is designed for board-certified general surgeons who want to continue in the practice of general surgery but who wish to expand their surgical knowledge to include thoracic surgery to enable them to meet emergency demands and to familiarize themselves with recent advances in this specialty.

The course will be given at Valley Forge Army Hospital, Phoenixville, Pa., and Brooke Army Hospital, Fort Sam Houston, Texas. Assignment of officers to this training will be on a permanent-change-of-station basis. Army officers interested should apply to the Army Surgeon General, Washington 25, D. C., Attn: MEDCM.

NAVY

Corpus Christi Hospital Welcomes Medical Society.—Capt. Thenton D. Boaz, M. C., U. S. Navy, commanding officer, U. S. Naval Hospital, Corpus Christi, Texas, welcomed the Nueces County Medical Society at a joint meeting April 10 at the U. S. Naval Air Station, Corpus Christi. Captain Boaz and his executive officer, Capt. L. G. Bell, M. C., received the members of the medical society at a dinner in their honor. Commander Ivan D. Baronofsky, head, thoracic and cardiovascular service, U. S. Naval Hospital, San Diego, Calif., spoke on "Present Status of Cardiovascular Surgery." The meeting was attended by 135.

Captain Ferwerda Accepts Clinical Directorship.—Capt. Thomas Ferwerda, M. C., U. S. Navy, retired, has accepted a position as clinical director at the Austin State School for Handicapped Children, Austin, Texas, which has an enrollment of about 2,000 patient-students and a staff of about 450 personnel. He is currently residing in his quarters at the Austin school.

SECRETARY OF DEFENSE

Lifetime Income Available Through Reserve Retirement.—According to the U. S. Navy Bureau of Medicine and Surgery, any person who has completed 20 years of "satisfactory federal service" as a commissioned officer, warrant officer, flight officer, or enlisted person in any branch of the Armed Forces or their Reserve components is eligible, on application, to receive retirement pay on or after reaching age 60, subject to certain conditions. The principal authority for this nondisability retirement is Public Law 810 (80th Congress), as modified by the Armed Forces Reserve Act of 1952.

While the last eight years of qualifying service must have been served as a member of a Reserve component, it is not required that this eight years be continuous. Service in the Retired Reserve is not creditable for this purpose unless such service was on active duty. The reservist or former serviceman concerned must not be eligible for, or receiving, any other retired pay for military service.

A member of a Reserve component before Aug. 15, 1945, must have performed active federal service during a portion of either of the following periods: April 6, 1917, to Nov. 11, 1918, or Sept. 9, 1940, to Dec. 31, 1946.

The rate of retirement pay is the number of accrued retirement points divided by 360 and multiplied by 2.5% times the applicable base pay of the rank or rating in which retired. Maximum pay is 75% of the basic pay.

PUBLIC HEALTH SERVICE

Indian Health Advisory Committee.—The U. S. Public Health Service has appointed an advisory committee on Indian health to assist in the improvement and expansion of medical care and health services to American Indians. The nine-member council will evaluate the Public Health Service's new Indian health program and assist in developing sound operating policies.

Three of the committee's members are themselves Indians. They are N. B. Johnson, Chief Justice, Supreme Court of Oklahoma; Mrs. Anna Wauneka of Window Rock, Ariz., chairman, Navajo Tribal Council's health committee; and Mr. Frank Ducheneaux of Cheyenne Agency, South Dakota, chairman of the Cheyenne River Sioux Tribal Council. The other members are Mr. Robert B. Atwood, editor and publisher, Anchorage *Daily Times*, Anchorage, Alaska; Dr. Robert Neff Barr, secretary, State Board of Health, Minneapolis; Dr. Fred T. Foard, state board of health, Raleigh, N. C.; Dr. Alexander H. Leighton, professor of psychology, School of Industrial and Labor Relations, Cornell University, N. Y.; Dr. James Perkins, director, National Tuberculosis Association, New York City; and Dr. Raymond F. Peterson, Butte, Mont.

Joint Sanitary Engineering Courses.—The first joint training courses for reserve sanitary engineer officers of the commissioned services—Army, Navy, Air Force, and Public Health Service—are scheduled to be given at the Public Health Service Robert A. Taft Sanitary Engineering Center in Cincinnati in June. Developed by the Department of Defense and Department of Health, Education, and Welfare, in collaboration with the National Research Council, these courses are designed for reserve engineer officers normally on inactive status. The courses will provide them with the latest information on sanitary engineering emergency operations applicable to situations in natural disasters and in military and civil defense emergencies. Two identical courses are scheduled, June 4-16 and June 16-29, each to be attended by 25 to 30 officers called to active duty by their own services. On June 16 a joint session will be attended by five special guests representing groups that have been particularly interested in development of the program.

MISCELLANEOUS

Anniversary of Food and Drug Act.—The Smithsonian Institution and the Food and Drug Administration jointly announce the opening of an exhibit commemorating the 50th anniversary of the passage of the original Federal Food and Drugs Act, which was signed by President Theodore Roosevelt on June 30, 1906. The exhibit in the Smithsonian's gallery of medical history in Washington, D. C., was opened May 4 at ceremonies, and among those expected to participate was Mrs. Harvey W. Wiley, widow of the man who was being honored as the father of the Pure Food and Drug Law.

The exhibit highlights the story of the 23-year battle by Dr. Wiley to secure a federal law that would curb the sale of contaminated foods and harmful drugs. In 1883, when Dr. Wiley became chief of the Bureau of Chemistry of the U. S. Department of Agriculture, one of his first official acts was to assign chemists to study food adulteration. Their work was reported in the bureau's famous "Bulletin 13," a 1,400-page document issued in 10 parts, covering 15 years of research.

This period was the heyday of "patent medicines." Typical products, shown in the Smithsonian exhibit, carried extravagant claims of effectiveness for every disease known to man. Labels gave no hint of the presence of dangerous or habit-forming ingredients; warnings against excessive use or misuse were unheard of; and ineffective products were labeled as sure cures for the most serious conditions.

A section of the exhibit shows improvements brought about by the Federal Food, Drug, and Cosmetic Act of 1938 (the present law). Under this law, official standards were established for food products; safety of new drugs must be proved before they are put on sale; medical devices and cosmetics are required to be safe and to bear truthful labels; and warnings against misuse are required on drug labels.

Another section of the Smithsonian display features special tools used by food and drug inspectors for sampling various products, including equipment for detecting filth-contaminated foods by ultraviolet light and portable scales used to check the net weight of packaged products.

The new exhibit is located in the Smithsonian's Arts and Industries Building, Ninth Street and Jefferson Drive S. W. It will be open to the public for the remainder of the year.

DEATHS

Gardner, Emily ⊕ Richmond, Va.; born in Franklin June 30, 1899; Woman's Medical College of Pennsylvania, Philadelphia, 1922; associate professor of pediatrics at the Medical College of Virginia; certified by the National Board of Medical Examiners; specialist certified by the American Board of Pediatrics; member of the American Academy of Pediatrics; at one time vice-president of the Richmond Academy of Medicine; chairman of the city board of health; served as a member of the state board of medical examiners and as president of the Richmond Tuberculosis Association; in 1950 named chairman of a new medical advisory committee of the Richmond Chapter of the National Foundation for Infantile Paralysis; chairman of the coordinating committee on crippled children's services of the Virginia Council on Health and Medical Care; from 1924 to 1929 assistant director of the bureau of child health for the state health department; at one time vice-president and secretary-treasurer of the Virginia Pediatric Society; in 1931 received the Mary Putnam Jacobi fellowship awarded annually by the Medical Women's Association of New York City; on the staffs of the Retreat for the Sick, Evangeline Booth Home and Hospital, and Sheltering Arms Hospital; died in the Medical College of Virginia Hospital Division Jan. 23, aged 56, of carcinoma of the lung.

Schoeneck, Henry William ⊕ Syracuse, N. Y.; born in Syracuse in 1884; Syracuse University College of Medicine, 1911; professor emeritus of obstetrics at his alma mater; specialist certified by the American Board of Obstetrics and Gynecology; member of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons; past-president of the Syracuse Academy of Medicine; director, bureau of maternal hygiene, health department; on the staff of the Syracuse Memorial Hospital; consultant, St. Joseph and City hospitals and Onondaga Sanatorium; died Jan. 22, aged 71, of myocardial infarction and coronary thrombosis.

Lee, Walter Nordal, Claremont, Calif.; born Feb. 16, 1887; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1909; an associate member of the American Medical Association; member of the Minnesota State Medical Association; formerly practiced in Madison, Minn., where he was for two terms mayor, for 20 years city health officer, for 35 years member of the staff of Ebenezer Lutheran Hospital, and first president of the Kiwanis Club; honorary member of staff of San Antonio Community Hospital in Upland; veteran, World War I; died Jan. 28, aged 68, of hypostatic pneumonia and cardiovascular disease.

Levitas, Matthew Samuel, Brooklyn, N. Y.; born in Newark, N. J., in 1892; Long Island College Hospital, Brooklyn, 1916; member of the Medical Society of the State of New York; at one time on the faculty of his alma mater; served in France during World War I; past national surgeon general of the Veterans of Foreign Wars; an assistant attending surgeon at Maimonides Hospital; formerly associated with Cumberland and Israel Zion hospitals, the Brooklyn Cancer Institute, Infants Home of Brooklyn, and the Brooklyn Jewish Home for Convalescents; died in the Veterans Administration Hospital, Fort Hamilton, Feb. 20, aged 63.

Abowitz, Jacob, Irving Texas; born in 1879; Fordham University School of Medicine, New York City, 1917; an associate member of the American Medical Association; member of the California Medical Association, Radiological Society of North America, and American College of Radiology; specialist certified by the American Board of Radiology; formerly practiced in Los Angeles, where he was for many years chief roentgenologist at the Cedars of Lebanon Hospital; chief roentgenologist, City of Hope National Medical Center, Duarte, Calif.; died in Dallas Feb. 24, aged 77, of myocardial infarction.

⊕ Indicates Member of the American Medical Association.

Barnum, Kenneth Raymond, Kansas City, Mo.; Hahnemann Medical College and Hospital, Philadelphia, 1908; served during World War I; died March 23, aged 71, of arteriosclerosis and hemiplegia.

Barton, Hugh Pierce, Chicago; Northwestern University Medical School, Chicago, 1910; served during World War I; formerly practiced in Davenport, Iowa, where he was on the staff of the Mercy Hospital; died April 12, aged 70, of coronary occlusion and arteriosclerosis.

Black, Claude Smith ⊕ Warren, Ind.; Medical College of Indiana, Indianapolis, 1905; past-president of the Indiana State Medical Association, Huntington County Medical Society, and the Eleventh District Medical Society; for many years councilor for the Eleventh District; served during World War I; a director of Blue Shield; on the staff of the Marion (Ind.) General Hospital, where he died March 28, aged 75, of gastric ulcer with hemorrhage and diaphragmatic hernia.

Blodgett, Clements Winfield, Syracuse, N. Y.; Syracuse University College of Medicine, 1913; for many years on the faculty of his alma mater; on the staff of the University Hospital of the Good Shepherd; died in the Syracuse Memorial Hospital March 20, aged 71, of burns suffered in a house fire.

Caron, Amable Berthelot, Woonsocket, R. I.; School of Medicine and Surgery of Montreal, Faculty of Medicine of the University of Laval at Montreal, Canada, 1900; served as city physician and school medical inspector; for many years practiced in Fall River, Mass.; died in the Woonsocket Hospital March 17, aged 81, of carcinoma of the left lung.

Carter, Earle Buel ⊕ West Hartford, Conn.; Johns Hopkins University School of Medicine, Baltimore, 1911; served as medical examiner for Connecticut for the Mutual Life Insurance Company of New York and also the Northwestern Mutual Life Insurance Company; on the staff of the Hartford Hospital, where he died March 19, aged 70, of coronary thrombosis.

Cowan, Harry Clayton ⊕ Walla Walla, Wash.; University of Michigan Medical School, Ann Arbor, 1916; died March 9, aged 65, of gastric ulcer.

Davis, Willa May Fricke, Baltimore; Johns Hopkins University School of Medicine, Baltimore, 1912; entered Mayo Foundation in Rochester, Minn., in 1915 and left in 1918; for many years associated with the Sinai Hospital; died in the Mercy Hospital March 8, aged 70, of arteriosclerotic cardiovascular disease.

Giardina, Nunzio Savior, Lorain, Ohio; Ohio State University College of Medicine, Columbus, 1927; member of the Ohio State Medical Association; on the staff of St. Joseph Hospital; died March 1, aged 57, of myocardial infarction.

Giesen, Allan Francis ⊕ Starbuck, Minn.; University of Minnesota Medical School, Minneapolis, 1925; member of the American Academy of General Practice; served during World War II; chairman of the school board; served on the village council and as mayor; died in the Northwestern Hospital, Minneapolis, Jan. 28, aged 52, of multiple myeloma.

Goorwich, Mary ⊕ New Orleans; Tulane University of Louisiana School of Medicine, New Orleans, 1922; member of the American Society of Anesthesiologists and the International Anesthesia Research Society; for many years on the staff of the Touro Infirmary, where she died Feb. 29, aged 61, of carcinoma of the kidney.

Greene, Edward Miller ⊕ Pawtucket, R. I.; Harvard Medical School, Boston, 1888; member of the Massachusetts Medical Society; for many years practiced in Boston, where he was on the staff of the Carney Hospital; formerly on the faculty of his alma mater; died in North Providence Feb. 29, aged 95, of arteriosclerosis.

Guest, Adolphus W., Chula Vista, Calif.; Western University Faculty of Medicine, London, Ontario, Canada, 1897; served during World War I; fellow of the American Psychiatric Association; at one time superintendent of the North Dakota State Hospital in Jamestown, and on the staff of the Athens (Ohio) State Hospital; died in San Diego Feb. 20, aged 86, of cerebral vascular accident and generalized arteriosclerosis.

Hale, Frank M., Ballinger, Texas; Barnes Medical College, St. Louis, 1905; served during World War I; football team physician for the Ballinger High School; died Dec. 7, aged 86.

Hansen, Walter J. ✠ St. Joseph, Mo.; Ensworth Medical College, St. Joseph, 1895; Bellevue Hospital Medical College, New York City, 1896; past-president of the city board of health; served as deputy state commissioner of health; veteran of World War I; died in the State Hospital number 2 March 19, aged 81, of myocarditis.

Harkins, John Patrick ✠ Portage, Wis.; Chicago College of Medicine and Surgery, 1915; past-president of the Columbia-Marquette Adams Counties Medical Society; served overseas during World War I; on the staff of the Divine Savior Hospital; died March 9, aged 64, of coronary thrombosis.

Harper, Aubrey ✠ Wray, Ga.; Southern Medical College, Atlanta, 1898; for many years postmaster of Wray, and a member of the county school board; died Feb. 20, aged 84, of bronchopneumonia.

Jones, Don Paul ✠ Plainview, Texas; St. Louis University School of Medicine, 1917; served in France during World War I; died in the Plainview Hospital and Clinic Feb. 27, aged 64, of hemorrhage of the esophagus and stomach.

Jones, Lawson D., Talihina, Okla.; Gate City Medical College, Dallas, Texas, 1908; died in the Memorial Hospital, Poteau, Feb. 18, aged 78, of coronary disease.

Judd, Loyd Wesley, Jr. ✠ Prague, Okla.; University of Oklahoma School of Medicine, Oklahoma City, 1950; interned at St. Anthony Hospital in Oklahoma City; served during World War II; died in the Oklahoma Medical Research Foundation Hospital, Oklahoma City, March 4, aged 33, of leukemia.

Koenemann, Stacy Lippincott Pancoast, Jr., Avoca, N. Y.; University of Toronto Faculty of Medicine, Toronto, Canada, 1931; an associate member of the American Medical Association; past-president of the Steuben County Medical Society; health officer of the towns of Wheeler, Howard, and Avoca; on the staff of the Bath (N. Y.) Memorial Hospital; died Feb. 29, aged 51, of multiple sclerosis.

Krugman, Bertram ✠ Jamaica, N. Y.; University and Bellevue Hospital Medical College, New York City, 1919; at one time on the faculty of his alma mater; served with the health department in Queens from 1920 to 1950, and for much of that time was head of the bureau of preventable diseases of Queens; affiliated with the St. John's Long Island City Hospital in Long Island City, and the Mary Immaculate Hospital and Jamaica Hospital; died March 19, aged 60, of coronary sclerosis.

Leimdorfer, Alfred, Chicago; Medizinische Fakultät der Universität, Vienna, Austria, 1910; research professor of pharmacology at Stritch School of Medicine of Loyola University; member of the American Heart Association; died April 9, aged 68, of coronary thrombosis.

Levington, Henry Lazaron ✠ Savannah, Ga.; University of Georgia Medical Department, Augusta, 1919; fellow of American College of Surgeons; served as president of the Georgia Medical Society; consultant at the Charity Hospital; on the staffs of the Telfair and St. Joseph's hospitals and the Warren A. Candler Hospital, where he died Feb. 28, aged 60, of hypertension and aortic insufficiency.

McBride, George Edmund, Magna, Utah.; University Medical College of Kansas City, Mo., 1906; served during World War I; died March 7, aged 75.

McComb, Edwin C., New Castle, Pa.; Western Reserve University Medical Department, Cleveland, 1898; an associate member of the American Medical Association; died Feb. 29, aged 85, of arteriosclerosis.

McGill, Ernest Charles ✠ Evanston, Ill.; Rush Medical College, Chicago, 1917; fellow of the American College of Surgeons; on the staff of St. Francis Hospital; died in the Veterans Administration Hospital, Downey, March 31, aged 66, of pulmonary edema and arteriosclerotic heart disease.

McNeill, Charles, Cedar Rapids, Iowa; Keokuk (Iowa) Medical College, 1897; for many years practiced in Quincy, Ill.; died March 22, aged 90, of heart disease.

Mandel, Sidney Norton ✠ Union City, N. J.; L.R.C.P., of Edinburgh, L.R.C.S., Edinburgh, and L.R.F.P. & S., Glasgow, 1939; interned at the Sydenham Hospital in New York City; served during World War II; on the staffs of the Fairmount and Margaret Hague Maternity hospitals in Newark and the North Hudson Hospital in Weehawken; died Feb. 12, aged 42, of coronary disease.

Moore, James Ross ✠ Los Angeles; Western Reserve University Medical Department, Cleveland, 1900; fellow of the American College of Physicians; member of the Central Neuropsychiatric Association; for many years member of the state lunacy commission; since 1925 member of the Hollywood Presbyterian Hospital and since 1921 senior consultant in neurology to the Los Angeles County General Hospital; died Feb. 3, aged 82, of acute myocardial infarction and arteriosclerosis.

Oden, John Wesley, St. Petersburg, Fla.; University of Nashville (Tenn.) Medical Department, 1908; an associate member of the American Medical Association; member of the Medical Association of Georgia; specialist certified by the American Board of Psychiatry and Neurology; formerly superintendent of the state hospital in Milledgeville, and the Georgia Training School for Mental Defectives at Gracewood, Ga.; died Feb. 20, aged 69, of cerebral hemorrhage.

Quinn, James Henry ✠ Springfield, Mass.; Georgetown University School of Medicine, Washington, D. C., 1907; fellow of the American College of Physicians; received the Distinguished Service Cross and three citations during World War I, in which he served as a major in the U. S. Army; a member of the board of trustees of the Springfield Municipal Hospital; on the staffs of the Westfield (Mass.) State Sanatorium and Mercy Hospital, where he died March 8, aged 73, of arteriosclerotic heart disease with congestive failure.

Regan, Alfred, Buffalo; University of Buffalo School of Medicine, 1907; for many years associated with the old city health department, retiring in 1946; an examiner for the Metropolitan Life Insurance Company; died Jan. 23, aged 72, of carcinoma of the head of the pancreas.

Reid, Wells Cook ✠ Goodrich, Mich.; Washington University School of Medicine, St. Louis, 1912; fellow of the American College of Surgeons; served overseas during World War I; for many years member of the school board; an elementary school in Goodrich was named for him; for 35 years superintendent of the Goodrich General Hospital; died Feb. 26, aged 69, of congestive heart disease.

Seidenstein, Jacob Leonard ✠ Saranac Lake, N. Y.; University and Bellevue Hospital Medical College, New York City, 1928; specialist certified by the American Board of Ophthalmology; served during World Wars I and II; on the staffs of Sanatorium Gabriels in Gabriels, Lake Placid (N. Y.), Memorial Hospital, Mercy General Hospital, Tupper Lake, and the General Hospital; died Feb. 27, aged 55, of acute myocardial infarction.

Stephenson, William Linus, Woodruff, Wis.; Wisconsin College of Physicians and Surgeons, Milwaukee, 1895; member of the State Medical Society of Wisconsin; died Dec. 28, aged 82, of acute coronary disease.

Sullivan, Robert Cecil ✠ Ardmore, Okla.; Vanderbilt University School of Medicine, Nashville, Tenn., 1922; fellow of the American College of Surgeons; on the staff of the Hardy Sanitarium; died March 30, aged 58, of coronary thrombosis.

Veselsky, Stanley R., Chicago; Dearborn Medical College, Chicago, 1905; died Dec. 12, aged 67, of arteriosclerotic heart disease.

FOREIGN LETTERS

BRAZIL

Infant Deaths in Cesarean Section.—Neme and Maretti, of the obstetric department of the São Paulo State University, reported at a recent meeting of the Associação Paulista de Medicina on the mortality of infants delivered by cesarean section at the university hospital during the period 1931 to 1952. Of 887 infants delivered by cesarean section, 19 (2.2%) were stillborn and 58 (6.5%) died immediately after birth. The indications for cesarean section that corresponded to the highest percentages of neonatal deaths were premature separation of a normally inserted placenta (80%); placenta previa (22.5%); contracted pelvis (4.2%); and prolonged labor (2.5%). The principal cause of death of newborn infants was asphyxia, the chief cause of which was placenta previa. General anesthesia was associated with a high percentage of neonatal deaths, since it is used in severe cases of placenta previa and regional anesthesia is contraindicated in cases of hemorrhagic shock in which fetal vitality is diminished. There was a higher percentage of neonatal deaths when the labor lasted 12 hours or less, and a higher percentage of stillbirths when the labor lasted 24 hours or more. There was a higher percentage of neonatal deaths in cases with unruptured membranes usually associated with placenta previa. The percentage of neonatal deaths was higher in infants of multiparas, and especially in those with over six children, coinciding with a high incidence of placenta previa in such patients.

Megaesophagus.—Köberle and Nador reported in *Revista paulista de medicina* (**47**:643, 1955) on the examination of serial sections of megaesophagus in seven patients. The incidence of megaesophagus is high in the Brazilian hinterland because of its association with American trypanosomiasis. The authors described several types of inflammatory esophageal lesions including pseudocysts of the Leishmania form of the parasite in the circular musculature. It is much more difficult to find the parasites in the esophagus than to find them in the myocardium.

Pneumonia in Children.—Vaněk and Jirocev observed 16 cases of parasitic pneumonia in children about 3 months old who either had been premature or were debilitated by sickness. The causative organism was the protozoan Pneumocystis carinii. This infection is nearly always fatal. Foam-like masses composed of the parasites form in the alveoli and bronchioles. Rabbits, guinea pigs, cats, dogs, sheep, and goats constitute a reservoir of the infection. The mode of transmission is still uncertain.

FINLAND

Prophase Index in Gynecologic Cancer.—The most constant difference in cancer of the female genital tract as compared with the corresponding normal tissue is a change in the relative duration of the various mitotic phases. Dr. Timonen compared the relative frequency of observance of the metaphase and prophase in biopsy specimens taken from the uterine cervix and corpus and the ovaries and reported his results in *Annales chirurgiae et gynecologiae Fenniae* (vol. 44, pt. 4, 1955). The prophase index is obtained by determining the ratio of observance of the metaphases to that of the prophase in a random sample of 100 cells. The author's series consisted of 80 patients with carcinoma, 43 with other pathological conditions, and 30 with normal tissues. The prophase index in noncancerous tissue varied between 0.3 and 1.5, and in cancerous tissue between 1.5 and 23. No sharp division between the index of benign and malignant tissue was observed. Because no prophase index determination gives pathognomonic values, it is advisable to classify the index values into three groups: low (under 1.5), moderately high (1.5 to 3.5), and high (over 3.5). Values near 1.5 have little or no diagnostic value. The values found in borderline cases (leucoplakia, carcinoma in situ, adenomatous hyperplasia, and malignant adenoma) were good indicators of the subsequent course of the disease. The prophase index values found in noninvasive and invasive carcinoma did not differ significantly. Both the histological and cytomorphological patterns were most atypical in the patients in whom the index values were highest. A correlation was established between the prophase index and the cytomorphological differentiation. The determination of the index may have diagnostic value in patients in whom the histological diagnosis is uncertain.

Melanoma of the Skin.—Dr. Brandt analyzed the records of the histopathological laboratories of Finland for a three-year period in an attempt to estimate the incidence of melanoma in relation to other malignant tumors (*Annales chirurgiae et gynaecologiae Fenniae*, vol. 45, supp. 3, 1956). In a series of 241 adults and 8 children with pigmented skin tumors in whom a primary histological diagnosis of malignancy or suspected malignancy had been made and 231 patients with a primary diagnosis of nevus, the primary diagnosis in a relatively large number was incorrect. Of the 194 patients with malignant melanoma in this series, 179 were followed up over three or more years (112 over a five-year period). In 28 patients, the lesion was located on the foot; of these, 26 have died. In six patients with melanoma and in two with cellular blue nevi, some other histologically verified malignant tumor was also present. As a rule, treatment consisted of local excision and postoperative irradiation, but some patients were treated only surgically and others only radiologically. After five years, 23 of 112 patients were alive; 100 patients died within two years after the histological diagnosis was made. Of the seven patients with cellular blue nevi, one died of a concurrent malignant tumor. Of the 10 children in this series with histologically malignant tumors, 2 had malignant melanoma (and died), 7 had benign juvenile melanoma, and one had a tumor showing infiltrative growth, although it was otherwise histologically benign (the clinical course in this patient was benign).

Carcinoma of the Lung.—Peräsalo and his co-workers present a series of 716 patients with pulmonary carcinoma in *Duodecim* (**N**:1, 1956) and call attention to the symptoms, signs, and operative treatment of this disease. Thoracotomy was carried out in 39.5% and resection in 27.1% of the patients. Thus, primary inoperability amounted to 60.5%. Postoperative complications were present in 25.3%, and the operative mortality was 10.3%. Pneumonectomy was performed on 183 and lobectomy on 11 patients. Bronchoscopy with endobronchial biopsy led to correct diagnosis in about 50%. In 12.9%, the diagnosis was made at exploratory thoracotomy. Only 1% of the patients were admitted during the silent phase of the disease. About 67% were admitted within six months of the first appearance of the symptoms and 10% within more than a year.

INDIA

Central Council of Health.—At the fourth meeting of the Central Council of Health, held at New Delhi in February, the Union Health Minister outlined the government's health program. The salient features of the program are to (1) provide adequate institutional facilities to serve as a basis for organizing health services, (2) arrange facilities for training medical and health personnel, (3) control communicable diseases that affect large sections of the community, (4) provide environmental sanitation, and (5) organize and assist a program of family planning and population control. The second Five Year Plan provided for an expansion of hospital accommodations, including accommodations for the staff, so as to provide better service. By the end of 1960 there will be an increase of 25% in the

number of institutions and 15% in the number of beds. Arrangements were made to set up more medical colleges. The training of more nurses, midwives, pharmacists, sanitary inspectors, and other technicians was planned. The program of malaria control envisaged the institution of 200 units, and, by the end of the second Five Year Plan, all the malarial zones will be covered. Regarding tuberculosis, the primary emphasis is on prevention by extensive use of BCG vaccination, the provision of clinics, the organization of domiciliary treatment, the institution of demonstration and training centers, and increased provision for isolation and rehabilitation. The family planning program that was started in the first Five Year Plan will be continued on a substantially increased scale. Environmental sanitation will have special priority. Preventive and curative pediatrics will be taught to undergraduate and postgraduate medical personnel and nurses in four regional centers. It is hoped to provide control units for leprosy in 135 districts where the incidence of this disease is high. Provision has been made for control of venereal diseases in all state programs. Four additional research and treatment centers will be started to fight cancer. More dental colleges will be established.

Protein Requirements.—Phansalkar and Patwardhan (*Indian J. M. Res.* **44:**1 [Jan.] 1956) reported their observations on nitrogen metabolism in five healthy men aged 21 to 27. The levels of protein intake in the diet were just sufficient to maintain nitrogen equilibrium. The sources of protein were whole egg, a single cereal such as wheat, and a mixture of cereals and pulses in the respective experiments. Nearly 80% of the total dietary nitrogen was derived from the test protein. Twenty-four-hour samples of urine and feces were collected for estimations of total nitrogen. The volunteers were fed three times in a day in the laboratory under supervision. It was noted that the urinary nitrogen level was higher with the subject on a regimen of wheat alone than on whole egg, thus throwing the body into negative nitrogen balance during the wheat diet period. With a mixture of cereals and pulses, the urinary nitrogen level was lower than with whole egg. There were changes in fecal nitrogen that in many cases were unrelated to those in urinary nitrogen. The observations on wheat protein confirmed those published for American subjects, who are habituated to a higher level of nitrogen metabolism. The biological and egg replacement values of vegetable protein were higher when the latter was derived from mixed cereals and pulses than when it was derived from a single cereal such as wheat. Pulses are thus good supplements to cereal in improving the quantity of dietary protein. The minimum level of protein intake required to maintain nitrogen equilibrium was found to be 3.55 gm. of nitrogen per square meter of body surface.

Cobalt with Iron for Anemia.—K. U. Jhatakia (*J. of Indian M. A.* **26:**4 [Feb. 16] 1956) states that 25 patients with iron deficiency anemia were given iron and cobalt intravenously. The results were compared with those obtained by giving iron alone. The preparation used contained 100 mg. of saccharated iron oxide and 5 mg. of cobalt in 5 cc. ampuls. Seventeen of these patients had a microcytic hypochromic hyposaturation type of anemia, four had a macrocytic hypochromic hyposaturation type, and four had a normocytic hypochromic hyposaturation type. The probable cause in one patient was tuberculosis, in 11 was nutritional deficiency, in 9 was hookworm, and in 4 was hemorrhage. The bone marrow in all was normoblastic. The drug was given in doses of 2 cc. on the first day and the dose gradually increased to 10 cc. per day if no reaction appeared. In only one patient did the administration of the drug have to be stopped, and this was due to the appearance of severe back pain, vertigo, and flushing. Minor side-reactions, such as backache, vertigo, headache, nausea, rise in temperature, palpitation, and urticaria, appeared in a few patients. These were the same as those observed when iron alone was given. The results on the whole appeared to be better with the iron and cobalt combination than with iron alone.

Prednisone.—Divekar and Patel (*J. Postgrad. Med.* **2:**1 [Jan.] 1956) state that they used prednisone on eight patients with rheumatoid arthritis, two with systemic lupus erythematosus, three with hypersensitivity phenomena, one with ulcerative colitis, and three with nephrotic syndrome. The results obtained with this drug compared favorably with those seen with corticotropin and cortisone. As compared to the latter, it seemed to be four or five times as potent. This enhanced potency was not associated with any undesirable side-effects. Facial rounding, epigastric distress, and diuretic action were some of the side-effects noticed. In the patients with nephrotic syndrome, a prompt diuretic action was obtained. Prednisone was also found to be effective in patients with systemic lupus erythematosus and hypersensitivity phenomena, but its use is advocated only in those with intractable cases of the latter. It may be the drug of choice in the management of collagen diseases and nephrotic syndrome.

Anemia and Ancylostomiasis.—Daftary and Bhende (*J. Postgrad. Med.* **2:**44 [Jan.] 1956) report a series of 96 patients with ancylostomiasis in which 74 patients were anemic. Of these, 22 had a nutritional megaloblastic anemia. In the other 52 the marrow was normocytic in 21 and macrocytic in 8. Chronic blood loss caused by the parasite cannot be the only factor in producing anemia in these patients, as the severity of anemia does not show any relation to the degree of parasitism as judged by the egg count in the stools. Furthermore, removal of the parasites did not cure the anemia, and the anemia can be cured without deworming the patient by giving him iron. Defective diet was a causative factor in some of these patients. Achlorhydria aggravates such deficiencies. Heavy nematode infestation also leads to disturbance of protein digestion and can thus be one of the factors concerned.

SWEDEN

BCG Vaccination.—Since Prof. Arvid Wallgren introduced BCG vaccination to Sweden in 1927, it came as a surprise when he began to question the justification for mass vaccination of the tuberculin-negative members of a community. In *Nordisk medicin* (**55:**20, 1956), he emphasized the extent to which the tuberculosis situation has changed since 1927, when tuberculosis was much more common and resistance to it was much weaker than it is today. With a comparatively high standard of living, earlier diagnosis, more effective treatment, and a shift of the time of first infection from childhood to adult life, the risk of contracting a serious case of tuberculosis has now become small. Only a minute fraction of the persons now vaccinated with BCG is likely to be rescued from fatal tuberculosis. Because occasional deaths are attributable to BCG vaccination, Wallgren asks how soon the time will come when the risks outweigh the benefits of mass BCG vaccination. Whenever there is a serious risk of infection with tuberculosis, BCG vaccination is still indicated. The tuberculin-negative child in a tuberculous family and the probationary nurse and medical student are and should remain candidates for BCG vaccination. Vaccination done at birth is often still effective in children entering school and may well continue to be so for some time to come. The schoolchild, with his strong natural powers of resistance, is hardly in need of BCG vaccination. Wallgren would like to see a gradual discontinuation of BCG vaccination in children of school age, with vaccination continued if the parents specifically request it. Wallgren also favors continuing the giving of BCG vaccination to children at the age of leaving school and to candidates for military service.

Swedish Hospital in Korea.—In *Svenska Läkartidningen* for March 23, 1956, Dr. Sture Rödèn states that the Swedish Hospital in Korea was moved in May, 1955, to quarters several kilometers east of the center of Pusan. It continues to be under the jurisdiction of the U. S. Eighth Army. The hospital's staff consists of 90 Swedes (including 11 physicians and 35 nurses) and about 290 Koreans (including 10 physicians and 40 nurses). In addition to the 250 hospital beds, there is a polyclinic service that deals with about 53,000 outpatients every year. The largest blood bank in Korea is located in the hospital's laboratory, which provided 5,870 pt. of blood in 1955. Tuberculosis and the parasitic diseases dominate the clinical picture in the hospital.

In spite of the heavy physical labor of Koreans, arthroses and spondyloses are rare. Adenoma of the prostate, diseases of the urinary tract, the usual forms of arteriosclerosis, and diseases of the biliary passages are also rare. Traffic accidents and burns are numerous on account of the lighthearted optimism with which the typical Korean meets the problems of daily life. Malignant tumors are often seen in an advanced stage. Pilfering is common and troublesome, but it should be remembered that the prolonged occupation of Korea by the Japanese created a defensive attitude that found excuses for mulcting the foreign invader. In conclusion, the author states that none of the more than 1,200 Swedes who have served in this hospital has suffered from any serious injury or disease.

Cowpox with a Secondary Rash.—Endemic cowpox is not rare in Sweden, and during the autumn months it is seen occasionally in human beings. In *Svenska Läkartidningen* for March 16, 1956, Björnberg and Björnberg state that only about 25 cases of cowpox followed by a secondary rash have been reported. This suggests that such a sequel of cowpox must be rare, but in the past 25 years about 30 such cases have been observed by one of them in a rural district with a population of about 15,000. According to the literature, the interval between the onset of cowpox and the appearance of a secondary rash may be as short as 4 days or as long as 22 days, but the authors found this interval to be remarkably constant—about three weeks. Their patients were afebrile and, on the whole, fit for work, with itching as the chief symptom. The rash itself had a characteristic distribution, showing a preference for the hands, forearms, the legs below the knees, and the nape of the neck. It consisted of partially confluent papules of the size of a grain of rice. They were red or red-brown, and the rest of the skin was also red. This condition has probably often been misdiagnosed despite the fact that it is well defined and has a characteristic localization. Its recognition should be all the easier for the fact that the primary pock may still be visible when the secondary rash appears.

Mass Radiography.—The mass radiography surveys designed for the discovery of pulmonary tuberculosis continue to reveal such other ailments as heart disease, Boeck's sarcoid, and malignant tumors. Dr. Ake Boman (*Nordisk medicin*, March 1, 1956) has reported on such a survey carried out on 88% of the population of a county containing 185,000 persons. Most of the 683 cases of heart disease discovered at this examination were followed up by Boman. About 50 patients were subjected to cardiac catheterization and other special examinations, and at least 8 were operated on. Of the 74 patients with congenital heart disease, 9 had coarctation of the aorta, and 7 a septal defect. Rheumatic heart disease was diagnosed in 116, hypertensive heart disease in 245, and a combination of the two in 73 patients. Auricular fibrillation without other pathological findings was diagnosed in 22, and syphilitic heart disease in only 4 patients. Boman concludes that heart disease may be found in about 0.5% of the persons undergoing mass radiography but adds that even serious heart disease may escape detection by it.

TURKEY

Salmonella.—In the *Bulletin of Hygiene and Experimental Biology of Ankara Institute of Hygiene* (vol. 15, no. 2), Dr. Namik Aksoycan stated that seasonal sporadic typhoid and paratyphoid epidemics occur in all parts of Turkey. According to the Ministry of Health and Social Assistance, 51,802 cases of typhoid fever with 4,289 deaths and 2,218 cases of paratyphoid fever with 118 deaths were reported between 1940 and 1952. In 100 blood cultures, 185 stool cultures, 51 urine cultures, and 4 bile cultures, the author isolated Salmonella schottmülleri from 23 and S. typhosa from 10. All typhoid strains were xylose-negative and arabinose-negative. Of 52 samples of water from streams in and near Ankara, 13 were found to contain strains of S. schottmülleri, of which 3 had negative Vi antigens. From one stream, a strain of S. enteritidis was isolated.

UNITED KINGDOM

Health of the Elderly.—In the *British Medical Journal* of March 17, Hobson and Pemberton report on the health of the elderly living at home. Their series consisted of 192 men aged 66 years or over and 284 women aged 61 years or over. Cardiovascular conditions accounted for more disability than any other condition, and 18.2% of the group were to some extent disabled. Hypertension was prevalent, but so many of the hypertensive subjects were in good health that it is doubtful whether hypertension alone causes heart failure in the elderly. Other common disorders were uterine prolapse in the women and prostatic hypertrophy in the men. Hernia was also common, and 19% of the men wore a truss. Failing hearing and eyesight were so common as to be regarded as almost natural results of aging; more than 92% wore spectacles. An adequate, well-balanced diet appeared to be an important factor in preserving health, and the quality of the diet bore a direct relation to social class and whether or not an elderly person was living alone. A large proportion of those who continued working after the statutory retiring age seemed particularly cheerful and alert.

Decubitus Ulcers.—In the *British Medical Journal* of March 10, Dr. Bateman reports that in decubitus ulcers the established lines of treatment (washing pressure areas with soap and water, drying and applying alcohol to harden the skin, using dusting powders, and changing the patient's position at least five times daily) were changed six months ago. It was believed that the atrophic skin of the elderly patient was not helped by frequent rubbing. The present routine is to change the position of the patient at least five times a day, but to wash the skin as infrequently as possible. Pressure areas are washed with warm water only twice a week, or when soiled. Silicone ointment is smeared evenly on pressure areas twice daily for a week and then once daily, and 25 mg. of tolazoline with 50 mg. of vitamin C is given three times a day. The results indicate that this method reduces the nursing attention required, is low in cost, and is at least as effective as the conventional methods.

Mammary Prosthesis.—In the *British Medical Journal* of March 17, Dr. D. K. Lennox describes a prosthesis for use after mastectomy. A 9-cm. band of cotton is sewn to a 10 to 15-cm. circle of gauze, and an artificial breast is readily made by drawing the free margin of the band to a point. The substance of the prosthesis is provided by birdseed, about 6 oz. is used for a 36-in. brassiere. This prosthesis readily adapts itself to the shape of the brassiere, holding it in place as it is malleable, and the shifting movement of the seed particles allows adaptation to movements of the arm and body. This prosthesis is much more satisfactory than the commonly worn rigid prosthesis, which has little malleability, does not adapt to arm movements, and when displaced gives the breast an unnatural appearance.

General Practitioners in Hospitals.—A circular has been issued by the Department of Health for Scotland that proposes combining general practice and hospital work. It will probably be difficult initially to find hospital posts suitable for this part-time work. A correspondent in the *British Medical Journal* of March 17 believes that this scheme will help to solve the problem of staffing departments of some of the smaller hospitals. In most departments, a consultant requires assistance that under the present scheme is provided by residents. This has resulted in a surplus of residents who have found themselves "fully trained, middle-aged, and unemployed."

Office Records.—Backett and Maybin report a new system of keeping records in a small rural practice in Northern Ireland. Each folder, instead of containing the medical record of one person, contains the records of an entire family. This method has helped the physician to get a general picture on the family problems in relation to illness and eliminated reliance on re-questioning or memory. The number of files was greatly reduced and the system was particularly convenient when more than one member of a family visited the doctor.

CORRESPONDENCE

HARDSHIPS OF INDIAN MEDICAL MEN AND WOMEN TAKING RESIDENCY TRAINING IN UNITED STATES HOSPITALS

To the Editor:—Due to the cold war, the United States is still geared to a war economy. The medical men of the United States are subject to draft into the armed forces like civilians and are retained in them in large numbers. Hence, civilian hospitals are undermanned and quite a few of them had to shut down their wards because they could not procure adequate personnel. American hospitals could absorb all the doctors that foreign countries could send here in the residency division, where a physician stays in the hospital and works almost 24 hours a day taking care of bed patients and those who come to the clinics in exchange for board and lodging and a monthly honorarium so low that a dishwasher makes that much in a week. The excuse is that these doctors are learning their vocation. So many Indian doctors have complained that with their experience in India they are allotted to jobs in American hospitals that they did during the first or second year after their graduation. They seem to think that they are aimlessly drifting instead of learning something new in ideas and techniques. Then why do they not leave? The obvious answer is that they are hoping against hope that the future might remedy the situation. Hence, this investigation was undertaken. We find that American authorities will cooperate fully to make this program function better. It is imperative that the Indian Medical Association should work this out with the American Medical Association.

We sent this report to the American Medical Association Council on Medical Education, and we got the following reply from its Director, Dr. Edward H. Leveroos:

"We appreciate very much being given an opportunity to review the statement which you propose to release regarding residency training under the Exchange Visitors Program. The statement, I believe, is essentially sound and points up some problems that are of particular concern to graduates of your schools."

This report is primarily intended to bring out some of the disadvantages in this program. It must be said in fairness to those Indian doctors who arrived in this country in the early groups that they, by reason of their stay and occupation of responsibility in their surgical specialties, attained a good knowledge and proficiency in their subjects and that they will be a great asset to the medical faculties in the various medical schools in India. These, however, are a minority.

The residency training program is an old one, practiced by most institutions that have adequate facilities to train resident staff members in various specialties. This system was in existence much before the creation of national boards in the various specialties; however, after the creation of the various specialty boards, standards for residency programs were developed by the Council on Medical Education and Hospitals of the American Medical Association collaborating with the specialty boards. Only those hospitals that can meet these standards are approved for residency training. By this it is meant that only those residents that have put in the required period in training, in the board-qualified institutions, will be eligible to sit for the board examination in a particular specialty. Although certification by the board is not essential to practice in a particular specialty, certainly passing this examination adds to prestige of the practitioner among the members of the profession. The board, if it considers the working of the department in any particular hospital below the set standards, may withdraw its recognition for the training. Naturally, this entails the loss of prestige to the department and there will be fewer or no applicants to such a department. Among the requirements of the board to make a hospital recognized in a particular specialty are a certain minimum of bed strength in that specialty, a minimum number of operations performed each year, a minimum number of outpatient visits in that clinic, a teaching program, and a minimum number of conferences each year. Certain records are to be maintained, and those should be made available to the credentials committee of the specialty board at any time for their scrutiny. In some specialties, nine months of teaching in basic sciences is required. Most of the hospitals that have the above program and have the board recognition are recognized by the State Department for entertaining the foreign physicians among the resident staff under the Exchange Visitors' Program. This Exchange Visitors' Program is a new scheme that has come into existence since the end of World War II. This has been systematized and somewhat intensified since 1950.

A few physicians were given fellowships under the auspices of the Indian government and sent to the United States to study in various specialties. Their expenses were mostly borne by the Indian or American governments. They came here mostly as either traveling fellows or residential fellows, and they did not actually participate in the residency training program. Moreover, those who participated in the program happened to be permanent officials of the Indian government. The first group of nonofficial physicians from India were selected and sent under the sponsorship of the Indian Medical Association in 1951. About 15 doctors were sent to a few hospitals in New York, Iowa, and Montreal, Canada. This group may be considered as the first that participated in the Exchange Visitors' Program and joined in the residency training program. Since that time, each year more and more physicians have joined the residency training program. While a good number of these physicians have come through the sponsorship of the Indian Medical Association, there are several who have come through church agencies and some others by directly applying to the various institutions.

Each year an increasing number of doctors are coming to America from India. This has been possible because the sponsors, especially the Indian Medical Association, had a favorable report of the program both from the candidates who underwent the training and also from their employer institutions. This encouraged the institutions to offer more residencies to Indian doctors. From the official point of view, the delegations that came under the exchange leadership program to the United States, including seven directors of public health and the deputy director general of public health of India, were favorably impressed with the reports about the working of the program and recommended their governments send more doctors for training. From the practical viewpoint there are certain drawbacks to this scheme. 1. Any recognized hospital in the United States can apply to the State Department to include the hospital as a participant in the Exchange Visitors' Program. It was possible for some of the institutions to get this recognition even though they did not have adequate facilities to train the resident staff properly. 2. The residency training program is supervised by a committee of the American Medical Association. This body has defined in their aims and objects reasons why the foreign residents are entertained. Here, they unequivocally mentioned that since World War II the hospitals and their bed strength were doubled and yet the number of available residents did not increase. Therefore, half the number of the posts remained unfilled. Naturally, the most desirable places are always filled by the American nationals; the unfilled ones are offered to foreigners. Those are not the best places but second rate. Under the residency matching program, no institution is permitted to take foreign candidates without offering the position to an American candidate first. Usually the appointments are made by November of each year for a place that is to be filled by July of the subsequent year. Only if there are not enough applicants or if a chosen candidate withdraws because of a better offer elsewhere is the position available to a foreigner. 3. Usually there is only a one-year contract between

the employer hospital and the candidate for residency. The candidate even if he is willing to continue may be dropped the next year, and, if this happens, the candidate may seek a position much inferior to the previous one. This is possible under a much-condemned system called the "pyramid system" of residency, practiced by most of the good institutions in the United States. Under this system, the hospital employs more residents in the first year than should normally go into the second year. But, as there are fewer positions in the second year, some residents are dropped on the basis of competitive merit. Again, by the end of the second year some of these are dropped, so that by the final year of residency only one or two remain. The selection is presumably done purely on merit. But in practice, this does not happen and the chief very regrettably has to select the local man to the detriment of the foreigner. In a poll that was conducted by a "resident physician," this system was condemned by a large majority of both residents and teachers alike. This system is very detrimental to the foreign resident, especially in the field of surgery.

The chief of the service may not inform the resident regarding his nonextension until the end. Therefore, the candidate may not know that he has to seek a position at another hospital. By the time the candidate knows about this, the best positions are probably filled and the candidate may settle for a less merited place. Also, depending on the large medical centers are several satellite smaller institutions, which may not be able to get residents by themselves. To get their routine work done, these institutions are in some way affiliated to the medical center, and the resident rotates through these institutions. But, if any resident is dropped out from the better place, he is usually advised to go to these small places that have a dearth of doctors and will be happy to have him. But the experience in such institutions is of no value to the doctor. Sudden termination of residency means a dislocation of the candidate's plans; a foreigner may not be able to accumulate enough money for passage, and, as a passage may not be available by ship at short notice, the candidate may have to accept a humbler position and continue here.

In one department of Bellevue Hospital an examination was held by the chief of service for the resident staff members who were completing the first year of residency. About 15 candidates sat for the examination, and the results revealed that first came a national of Ireland and second an Indian. The examination was intended to choose the best for the second-year positions. The postings were first made accordingly. However, a protest was made by American candidates, and the plan was abandoned and both the first two candidates were given the least desirable positions. The Indian national was relegated to an inferior hospital with less pay and in a smaller position than he held the previous year. Recently some of the hospitals have put in new restrictions on foreign residents. Prior to 1950, Bellevue Hospital of New York employed foreigners on a "no stipend" basis while their native colleagues drew a minimum stipend of $60 per month. This order was removed in 1951, when there were not enough candidates to man the hospital as residents as a result of drafting medical men to serve in the Korean war. However, a new order came in 1954 that foreign residents may not be employed as chief residents. This law is discriminatory, as in several surgical specialties the main operative work is done only when one becomes a chief resident, which is in the third, fourth, or fifth years. There is one reason why Indian doctors are preferred to any other foreign doctor. In India the medium of instruction in the medical college is in English, and Indian doctors have a fair degree of proficiency in the language. This puts them at an advantage before a Latin American or any European doctor other than English.

If the Exchange Visitors' Program is to be successful, certain conditions must be fulfilled. 1. The training of the doctors should be confined to only the larger medical centers with adequate facilities. 2. Those who are accepted must be permitted to finish the complete residency. 3. They should not be permitted to change from hospital to hospital for any reason. 4. Those who are accepted must be recent graduates, must be young, and must be those who did not have any previous training in the specialty. 5. The candidates must be selected through an accredited agency such as the Indian Medical Association, so that properly suited candidates are selected. 6. It is desirable that they be given a better stipend and passage money, so that financial considerations do not weigh in choosing the hospital. 7. The program should be confined to a definite number each year and not as indefinite as it is practiced now. 8. Those who finish the third or fourth years' training must be returned home. The visa should not be extended for any reason.

My staff prepared the above study, and it was released as a dispatch to newspapers in India through my news service. I am happy that through THE JOURNAL interested Americans will have an opportunity to study this. After all, any improvement in this or any similar program will come about only through Indo-American cooperation, which I am interested in promoting in its various phases in my capacity as an editor and publisher of India.

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SODIUM CHLORIDE AND HYPERTENSION

To the Editor:—THE JOURNAL, March 17, page 997, carried my letter mentioning evidence that saltless diet can reduce puerperal eclampsia to the vanishing point. Newspapers now are informing the public of observations presented at the recent meeting of the American Society for Experimental Pathology at Atlantic City, N. J., showing that among 1,346 employees of the Brookhaven National Laboratory the incidence of essential hypertension was significantly related to the salt intake. This adds to the large growth of evidence supporting salt restriction for treatment and prophylaxis, which I have advocated since 1920. Negative arguments regarding saltless diet have been (1) that it fails to reduce the pressure in a group of "refractory" cases, though its similar failure to clear up many cases of advanced anasarca does not discredit its benefit for edema, and (2) that many hypertension cases are "benign" in the sense of being compatible with longevity; but these patients do generally die of arterial causes, and if they die in their 60's when they might have lived into their 80's the condition is scarcely benign. Some of the affirmative considerations are as follows. 1. No critic has followed these cases for years, as I have, to observe that the diet generally arrests progression and prevents complications even in the "refractory" cases. 2. Nobody can foretell which cases will turn out "benign" or otherwise. Formerly about 50% of hypertensive persons died of congestive failure, and competent authorities now corroborate my experience that this complication is positively prevented by saltless diet and life is prolonged for many years. I find retinopathy and the "malignant" phase also prevented. 3. Salt aggravates and even produces hypertension in experimental animals. In all medical literature there is no equal to the clinical disregard of this clear experimental proof. The overwhelmingly preponderant cause of death in the civilized world is arterial disease; namely, hypertension and arteriosclerosis. The conjunction of experimental and clinical hypertension, salt metabolism, and also lipid metabolism with the adrenals is plain. It is a problem of metabolism, not of cardiology. My belief is that a considerable proportion of the population is predisposed, so that this chemically and physiologically powerful substance acts as an exciting cause of hypertension and possibly contributes to atherosclerosis. A successful demonstration offers the means of largely eliminating the leading cause of disability and death. Trial must be made sooner or later, because of the experimental evidence and because there is no other prophylaxis in sight. The problem is certainly not to be solved by medical nostrums, surgical mutilations, or carefree living.

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MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Indications and Success of Peroral Treatment of Diabetes Mellitus with a Sulfonyl Carbamide Derivative: Report on 335 Patients. F. Bertram, E. Bendfeldt and H. Otto. Deutsche med. Wchnschr. **81:**274-278 (Feb. 24) 1956 (In German) [Stuttgart, Germany].

Nadisan, a proprietary preparation of N_1-sulfanilyl-N_2-n-butylcarbamide (BZ 55) was given to 335 patients with diabetes mellitus. The drug was administered orally in tablets of 0.5 gm., five tablets being given on the first day, four tablets on the second day, three tablets on the third, and two tablets on successive days. Occasionally higher initial doses up to six tablets daily were required for several days or weeks. In patients in whom the metabolism became balanced within a few days, an attempt was made to do with a 10-to-14-day course. Frequently treatment had to be continued for prolonged periods until the metabolism was restored to normal. But even then it seemed advisable to continue with the administration of the drug for several additional weeks, since the intervals during which no Nadisan was required were short. Patients in whom the metabolism could not be restored to normal were given a minimum maintenance dose.

The authors' first report on this new type of treatment of diabetes mellitus, an abstract of which was published in THE JOURNAL (**195:**1328 [Nov. 26] 1955), dealt with the influence of the patient's age and the duration of the disease on the effect of the treatment, but in the meantime it has been recognized that constitutional factors are of paramount importance for the success of the treatment. In contrast to the previous report, this one states that limited therapeutic success can probably also be obtained in patients of advanced age with long duration of the disease and in juvenile patients, provided that they are of the sthenic-pyknic type with a tendency to adiposis. The metabolism in these patients is less labile than in the typically asthenic, leptosomatic patients with "insulin deficiency diabetes." Hypoglycemic shock is rare in the sthenic patients. The treatment with Nadisan was effective if the patient had not previously been treated with insulin or had received this drug for only one or two years. After three years' treatment with insulin, satisfactory results with Nadisan may be expected in only 50% of the patients. The amount of insulin given previously has no relation to the effect of Nadisan if the patient responds to the latter drug. Of the 335 patients treated with Nadisan, satisfactory results were obtained in 218; 76 of these were followed up for more than two months and 34 for more than six months. Continued treatment with a small maintenance dose seemed to be advisable in most patients. In none did Nadisan cause resistance to insulin and in none was the effect of Nadisan reduced by repeated administration.

As a rule, Nadisan alone was ineffective in asthenic-labile patients with insulin deficiency diabetes, but it seems that combined treatment with insulin and Nadisan may occasionally exert a salutary effect on their metabolism. Nadisan might be effective in isolated cases of diabetes mellitus in asthenic patients with a labile course requiring small amounts of insulin. Constitutional factors also play an important part in the treatment of juvenile patients with diabetes mellitus, since several young patients of sthenic-pyknic type, whose metabolism was on the borderline of insulin deficiency, could, in contrast to those of the asthenic type, be controlled with Nadisan, but it seems unlikely that in the long run they will be able to go on without insulin. The tolerance to Nadisan was good even with high doses of the drug and with prolonged treatment. The exact mechanism of the action of Nadisan is unknown.

The Effect of a New Sulfonamide on Diabetes. E. Tolomelli, R. Pellegrini and A. Poppi. Riforma med. **70:**180-183 (Feb. 18) 1956 (In Italian) [Naples, Italy].

The authors studied the results obtained by treating diabetic patients with a new sulfonamide (BZ 55). This product, administered orally, has a definite effect on the blood sugar level. The lowering effect can still be noticed even more than 24 hours after the drug has been administered. The patients were subdivided into a group of younger people and one of older. None of them had had the disease for more than six years. BZ 55 does not seem to have a satisfactory result in juvenile forms of diabetes. The substitution of BZ 55 for insulin proved to be effective in older patients with diabetes. The drug seems able to maintain the metabolic status in a good balance even some time after the treatment has been terminated. The drug never caused a hypoglycemic crisis. It does not seem to cause addiction.

Duodenal Diverticulosis: Case Contribution and Clinical Considerations. G. P. Cenci and L. Lucentini. Policlinico (sez. med.) **63:**1-11 (Jan.-Feb.) 1956 (In Italian) [Rome, Italy].

On the basis of six of their own patients and of a review of the literature, the authors state that uncomplicated duodenal diverticulosis is almost always asymptomatic. It causes pain only when it is associated with complications such as inflammation, hemorrhage, and perforation, with the formation of diffuse peritonitis or of a subphrenic abscess. In some instances carcinoma may develop in the diverticulum, while in others there may be acute and chronic pancreatitis or atrophy of the pancreas. However, even when a duodenal diverticulosis becomes complicated it does not cause symptoms that are so characteristic as to lead to a correct diagnosis. One of the few diagnostic features of duodenal diverticulosis can be the fact that the condition occurs most frequently in aged persons with disturbances that can be ascribed to a painful digestive dyspeptic syndrome, a pancreatic syndrome, or a syndrome of the biliary ducts. Among the commonest symptoms are a feeling of heaviness and nausea with pain that differs from that of a gastroduodenal ulcer. Another diagnostic feature is the fact that poor general condition and asthenia, which are early signs of a gastric carcinoma, are not present, as a rule, in patients with duodenal diverticulosis. Of some diagnostic significance could be the presence of diarrhea. Gastric cancer is often associated with constipation. Despite these differential diagnostic criteria, in most instances a diagnosis of duodenal diverticulosis cannot be made on the basis of clinical data alone. It must rest on roentgenographic demonstration. Only after the presence of a duodenal diverticulosis has been demonstrated roentgenographically can the most suitable medical or surgical treatment be instituted.

Periarteritis Nodosa and Its Treatment with Corticotropin. L. -N. Larochelle and J.-M. Julien. Laval méd. **21:**164-174 (Feb.) 1956 (In French) [Quebec, Canada].

A 66-year-old man entered a hospital in a state of extreme weakness, emaciation, and anxiety caused by severe pain in the extremities of three weeks' duration. The patient also had chronic asthma, for which he had required hospitalization in the past. His limbs were atrophic and covered with hemorrhagic plaques. It seemed that he had purpura of the Schönlein-Henoch type. Hematological examination revealed marked leukocytosis and eosinophilia. A superficial biopsy showed that the purpura was

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The place of publication of the periodicals appears in brackets preceding each abstract.

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inflammatory. His condition was then diagnosed as purpura of allergic type secondary to periarteritis nodosa. The angiopathy was confirmed by muscle biopsy. The patient was treated with corticotropin given intravenously and Hydrocortone given orally. His general condition improved, pain was decreased, the purpura disappeared, and his temperature returned to normal. Eosinophilia dropped from 44 to 7%. The patient was given a few milligrams of prednisone on discharge from the hospital. Four months later, having received no therapy in the interim, he had to have another course of corticotropin therapy because of asthma and pain in the feet. Eight slow intravenous infusions of 20 mg. of the drug each reduced eosinophilia from 54 to 13% in 10 days. The patient was discharged once more and is being followed regularly.

Metacortandracin (Meticorten) in the Treatment of Disseminated Lupus Erythematosus and Periarteritis Nodosa. C. LeRoy Steinberg and A. I. Roodenburg. Ann. Int. Med. **44:**316-336 (Feb.) 1956 [Lancaster, Pa.].

The synthetic steroids have advantages over cortisone and hydrocortisone; not only is their anti-inflammatory effect several times more potent, but they avoid sodium retention and depletion of potassium, cause little or no disturbances in the protein and carbohydrate metabolisms, and are less likely to produce untoward reactions such as hirsutism, moonface, and gastric disturbances. The authors used Metacortandracin, now known as prednisone, in six patients with disseminated lupus erythematosus and three patients with periarteritis nodosa. The diagnosis of disseminated lupus erythematosus was confirmed in all instances by the finding of L. E. cells both in the bone marrow and in a two-hour clot test. In two of the patients with periarteritis nodosa the diagnosis was confirmed by biopsy and in one instance also by autopsy studies. The third patient with periarteritis nodosa was not subjected to biopsy, but his clinical course was so typical of the disease that there appeared to be no question of the diagnosis.

The autopsy in the patient with periarteritis nodosa who died during treatment showed extensive arterial involvement, both visceral and peripheral. The most remarkable feature in the histological study was the absence of inflammation in the diseased arteries. It is assumed that, if this patient had been treated in the early phase of the disease, the outcome would have been more favorable. The other two patients with periarteritis nodosa, who were very ill, are now able to work. All six patients with disseminated lupus erythematosus had previously been treated with either cortisone or corticotropin. In all of them prednisone proved more effective, although the L. E. cells did not disappear from either the bone marrow or the peripheral blood. All six patients lead active lives with little or no restrictions. The patients appreciate the fact that they can eat a normal diet without salt restriction or the addition of large doses of potassium, as required with the use of the other steroids.

The initial daily dose was 30 mg., given in three divided doses of 10 mg. each. The dose was decreased by 5 mg. every five days until the smallest amount required for maintenance was reached. It was usually 15 to 20 mg. per day. All except one of these patients have been observed under treatment for from 60 to 120 days. The short-term treatment has been favorable, but more time will have to elapse before a conclusive opinion can be reached as to long-term treatment of the collagen diseases with this new compound.

Pseudohemophilia: Report of 13 New Cases and Statistical Review of Previously Reported Cases. J. C. Buchanan and B. S. Leavell. Ann. Int. Med. **44:**241-256 (Feb.) 1956 [Lancaster, Pa.].

Pseudohemophilia is a hemorrhagic disorder, occurring in either sex, that is distinguished by a bleeding tendency and by the single laboratory abnormality of a prolonged bleeding time. This hemorrhagic diathesis was studied a quarter of a century ago by von Willebrand in 16 female and 7 male members of one family on the Åland Islands near Finland. Since then, similar cases have been reported under a multitude of names, including pseudohemophilia, von Willebrand's disease (constitutional hereditary thrombopathy), thrombocytic dystrophy, thrombasthenia, capillaropathy, thrombocytopathic purpura, and athrombocytopenic purpura. The authors review the literature and present 13 patients observed at the University of Virginia Hospital, bringing the total of reported cases to 199. The authors hope that the progress in understanding of clotting mechanisms will help to determine whether pseudohemophilia is a definite clinical entity.

Pseudohemophilia differs from other hemorrhagic states and does not fit into the classification of the "hemophilia-like" disorders. It occurs in both sexes and is often familial. The principal clinical manifestations are repeated episodes of abnormal bleeding. The only consistently abnormal laboratory finding is a prolonged bleeding time. The bleeding tendency and the bleeding time in a given patient are variable and unpredictable. Although bleeding episodes are common, the outlook for life is relatively good. The mechanism of the defect in hemostasis is uncertain and may not be the same in all cases. The cases may not all represent a single entity. There is some evidence for both a platelet defect and a vascular defect. There is no satisfactory specific therapy. Since any surgical procedure is a major hazard in these patients, all but the most urgent surgery should be avoided.

Hypervitaminization Therapy of Patients with Cancer and Evaluation of Their Defense Powers with the Aid of a Cutaneous Test. E. Schneider. Medizinische, No. 5, pp. 183-187 (Feb. 4) 1956 (In German) [Stuttgart, Germany].

One hundred seventy-two patients with cancer were treated at the district hospital in Lahr, Black Forest, Germany, with massive doses of vitamins A and C. The patients were given 1,000 mg. of vitamin C and 300,000 I. U. of vitamin A daily for periods up to six months. Although signs of hypervitaminosis A, such as drowsiness, vertigo, lassitude, irritability, and vomiting, were not observed in the course of continuous treatment, it seemed advisable to give weekly courses separated by weekly treatment-free intervals. Improvement of the general condition, increase of weight, and reduction of erythrocyte sedimentation rate were always observed, except in definitely cachectic patients. Although a complete cure could not be obtained, it seemed that during the treatment the disease progressed slowly, while after discontinuation of the vitamins rapid deterioration occurred. Six illustrative cases are described in a man and two women between the ages of 66 and 75 with inoperable cancer of the stomach with metastases in the liver, in a 33-year-old woman with carcinoma of the ovary, in a 76-year-old man with a metastatic hypernephroma in the upper arm, and in a 52-year-old woman with adenocarcinoma of the splenic flexure and ovarian metastasis. Treatment with massive doses of vitamin A and C was ineffective in patients with sarcoma.

Various healthy persons, 13 patients with benign tumors, 9 patients with cancer of the cecum, rectum, sigmoid, stomach, ovary, uterine cervix, and breast or lymphatic leukemia, and one patient with fascial sarcoma were subjected to a cutaneous test by intracutaneous administration of 0.5 cc. of lyophilized serum in isotonic sodium chloride solution obtained from normal persons, from untreated patients with cancer, and from patients with cancer treated with massive doses of vitamin A and C. The serum was obtained only from patients in whom inflammatory associated diseases could be excluded. As reaction to the serum, redness and particularly infiltration were evaluated. Results showed that healthy persons are insensitive to the lyophilized serum obtained from normal persons and from treated and untreated patients with cancer. The assumption that serum obtained from patients who had been treated for prolonged periods with vitamin C and A would produce milder cutaneous reactions in patients with cancer than the serum obtained from untreated patients with cancer was not confirmed. Occasionally the reaction to the serum obtained from vitamin-treated cancer patients was even more severe than that to the serum obtained from untreated patients. Despite uncertainties associated with the method, the presence or absence of a tendency to recovery could be determined to a certain extent in the patients with malignant tumors. A change in the reactivity to the test after surgical removal of the tumor and after treatment with massive doses of vitamin A and C can be explained only by the removal or the death of the cancer cells or by their spontaneous (enzymatic, autolytic) destruction. Since spontaneous cures of tumors are known, this possibility must be

considered, but the results of the cutaneous tests also gave definite proof of the presence of strong defense powers in the patients' bodies as suggested by Domagk. Reactions to the test were elicited in all types of tumors, carcinomas as well as sarcomas, and this observation suggests a common factor.

Hookworm Treatment of Polycythemia Vera. J. Myhre and F. Wallace. Minnesota Med. **39:**99-100 and A-40 (Feb.) 1956 [St. Paul].

Hookworm infestation has been used by investigators in other countries in the treatment of polycythemia vera, and so the authors resorted to this treatment in a 51-year-old woman who objected to the intermittent large volume blood loss of venesection. Polycythemia vera had been diagnosed in 1937, and since then the woman had been treated with phenylhydrazine and venesection. She was first seen by the senior author in March, 1951, when she was quite weak, and venesection therapy was begun again. In the eight months remaining in 1951, 1,900 cc. of blood was removed by venesection; in 1952, 3,200 cc; and in 1953, 2,000 cc. Before the venesection she was generally extremely uncomfortable and complained of headaches, fullness in the head, unsteadiness, clumsiness, and feeling flushed and weak, with scattered paresthesias. After the venesections the patient again felt quite weak.

The hookworm larvae used for treatment were identified as Ancylostoma duodenale. They were obtained from a stool specimen that was mixed with powdered charcoal and incubated at room temperature for two weeks. The mixture was then placed in a Baermann funnel, and the infective larvae were collected. The larvae were filtered out of the suspending water, and the filter paper, with the larvae down, was again placed on five layers of gauze on the screen of a Baermann funnel and the larvae were collected a second time in clean water. The larvae were suspended in 15 cc. of water, and from counts of 0.1-cc. samples an estimate of 260 larvae was made. The suspension was poured on a 3-in. disk of white blotting paper that was laid upon the patient's left thigh for one hour. The patient noticed mild local itching during the exposure. For the next 10 days there was a swelling and thickening of the inoculation site with a hive-like formation. Shortly after this respiratory infections developed, and one month after the larvae were introduced a severe night cough productive of a small amount of sputum developed and persisted for one month. Approximately six weeks after the administration of the larvae, the patient noticed morning nausea with occasional emesis. About two months later she had two or three loose stools daily, for a period of about two weeks. After that she felt well, better than she had felt in years. The ova first appeared in the stools 11 weeks after exposure; after 18 weeks 1,100 ova were counted. Since then monthly counts have averaged 3,500.

The treatment appears to be simple and inexpensive, and there does not appear to be a need for detailed supervision or special laboratory facilities. There is a slow regular fall in the red blood cell count. The therapy lasts five to six years, and treatment can be terminated at any time. The disadvantages are the diarrhea, which can persist up to two months but can be controlled by paregoric and, in this instance, a severe cough, which was the only apparent disadvantage after 14 months' observation.

Immunity to Malaria in African Negroes: Experimental, Epidemiological, and Statistical Evidence. P. Gallais and H. Collomb. Presse méd. **64:**161-164 (Jan. 28) 1956 (In French) [Paris, France].

The authors report 10 cases in which Negro patients with various neurological disorders, mostly of syphilitic origin, were inoculated with Plasmodium vivax as a therapeutic measure. Convulsive attacks of malaria could not be produced in any of these patients, although when the same strains of P. vivax were injected in European subjects, violent attacks of the disease occurred, sometimes necessitating interruption of this treatment. Slight reactions, with fever, occurred in two of the Negro patients, the only two who were not from Africa (one was from Madagascar and the other from Martinique). Seven other African Negro patients with neural syphilis were treated with no result, three with P. vivax and four with the more virulent P. falciparum, which is never used in white patients. During the war in Indo-China, it was noted that African Negro soldiers did not succumb to the malaria prevalent in the war area, while Europeans, North Africans, and Vietnamese were stricken in large numbers. None of the Negroes who had been prisoners showed signs of splenomegaly on liberation; hematozoa were found in only one. A survey of a French hospital shows that no patients with malaria in France are African Negroes. Thus it appears that their immunity to the disease is independent of geographical location, type of strain, changes in climate, way of life, dietary and vitamin deficiencies, and other stress factors.

SURGERY

Intraperitoneal Antibiotic Administration in the Treatment of Acute Bacterial Peritonitis. W. E. Schatten. Surg. Gynec. & Obst. **102:**339-346 (March) 1956 [Chicago].

Thirty-eight patients in whom acute diffuse peritonitis was demonstrated at the time of surgery were treated after operation by intraperitoneal administration of oxytetracycline or neomycin. Oxytetracycline was used in 20 patients and neomycin was used in the other 18. The antibiotic was instilled intraperitoneally through two small polyethylene catheters that were introduced into the peritoneal cavity through a 13-gauge needle at the time of operation. One catheter was directed into the pelvis along either the right or left lateral gutter and the other was directed over the right lobe of the liver to the region of the right subphrenic space. One gram of the antibiotic was mixed with 500 ml. of isotonic sodium chloride solution to provide a concentration of 2 mg. per milliliter, and 250 ml. was instilled through each catheter at the time of operation. Then 125 mg. of antibiotic in solution was instilled through each catheter every 6 hours for a maximum of 72 hours. The solution was allowed to run in at a rate of 80 to 100 drops per minute. The patients received 1 to 2 gm. of the antibiotic daily for one to three days. Peritoneal fluid was obtained for culture at the time of operation and every 24 hours thereafter by aspiration through the catheters just prior to instillation of the antibiotic (6 hours after a previous dose).

One or more organisms were cultured from peritoneal fluid, obtained at the time of operation, of 30 patients, despite the fact that preoperatively 14 of these patients had received large quantities of antibiotics intramuscularly. A positive peritoneal culture was obtained postoperatively in only one patient after the institution of intraperitoneal therapy with antibiotics. It is believed that the high levels of oxytetracycline and neomycin resulting from the intraperitoneal administration were responsible for sterilization of the peritoneal cavity. While three patients had clinical signs and symptoms of a pelvic abscess, the presence of such an abscess was proved in only one of the patients. Four deaths occurred; two were due to a pulmonary embolus and one was due to a complete occlusion of both coronary arteries. The other patient was almost moribund at the time of operation. The intraperitoneal instillation of tetracycline hydrochloride is contraindicated because of nausea, vomiting, and the formation of intraperitoneal adhesions. The intraperitoneal administration of oxytetracycline or neomycin is effective in treating patients with peritonitis. Intraperitoneal instillation of neomycin causes less discomfort than intraperitoneal instillation of oxytetracycline. Neomycin is considered the drug of choice for intraperitoneal administration.

Tetracycline (Achromycin)–Neomycin for Preoperative Colon Preparation. I. Cohn Jr. and A. B. Longacre. A. M. A. Arch. Surg. **72:**371-376 (March) 1956 [Chicago].

The authors found that the combination of tetracycline (Achromycin) hydrochloride–neomycin and the usual mechanical aids to cleansing the large intestine came closer to true sterilization of the feces than did any other agent or combination of agents tested. Patients were selected at random from the Louisiana State University Surgical Service of the Charity Hospital at New Orleans. The only requirement was that they not have any known disease of the gastrointestinal tract. They were placed on a low-residue diet, were given daily enemas and a cathartic

the first day of the program, and were given the tetracycline-neomycin combination as follows: four tablets every hour for 4 hours, then four tablets every 6 hours for a total of 72 hours. Each tablet contained 50 mg. of tetracycline and 250 mg. of neomycin; hence, the unit dosage was 200 mg. of tetracycline and 1.0 gm. of neomycin.

Quantitative bacteriological analyses were conducted on the stools. Three days of therapy rendered the stool almost sterile. Side-reactions were minimal. The absence of the disturbing gastrointestinal reactions that so frequently accompany the administration of broad-spectrum antibiotics in dosage that is adequate for bowel sterilization was a definite advantage. The outgrowth of yeasts, frequently blamed for many of the disturbing side-effects, did not reach significant proportions until the last day of preparation and therefore should not be a source of trouble. The return of the usual fecal flora, with its attendant decrease in the yeast count, has been another point in favor of this method of preparation of the large intestine. The over-all results with this type of preparation have been so satisfactory that the authors have adopted it as the standard method for all patients undergoing elective surgery on the colon.

Complications of the Surgical Treatment of Chronic Ulcerative Colitis. B. P. Colcock and W. L. Mathiesen. A. M. A. Arch. Surg. **72:**399-404 (March) 1956 [Chicago].

Colcock and Mathiesen reviewed the records of 307 patients with chronic ulcerative colitis who were subjected to ileostomy and colectomy between 1946 and 1954. They were chiefly concerned with the complications arising from the surgical management. In the seriously ill patient an ileostomy alone can be done with a lower mortality than ileostomy plus colectomy. However, in patients who are reasonably good operative risks, subtotal colectomy may be combined with ileostomy without increasing the operative mortality. Irritation of the skin surrounding the ileostomy occurred in 49 (15.9%) of 307 patients. This complication occurred in only 12 patients while they were still in the hospital, indicating the need for careful instruction regarding the care of the skin. Electrolyte imbalance occurred in 37 patients (12%). Careful attention to any alteration in the character or amount of the ileostomy discharge and adequate replacement of fluid and electrolyte loss during the early postoperative period will usually prevent serious electrolyte imbalance. Obstruction occurred in 134 patients (43.6%). Often, obstruction was temporary and was relieved by catheter irrigation of the ileostomy combined with intubation by the Miller-Abbott tube. In many instances the obstruction was the result of a partial stricture at the site of the ileostomy and was relieved by a minor surgical procedure.

Fistula formation occurred in 68 patients (22%). Prolapse of the ileostomy has been common in the past, but if care is taken to provide adequate fixation of the mesentery of the terminal ileum to the parietal peritoneum at the time the ileostomy is constructed, this complication will occur infrequently. Fixation is obtained by suturing the mesentery of the ileum rather than by placing sutures in the wall of the large intestine itself. Adequate fixation also tends to prevent retraction. Postoperative hernia at the site of the ileostomy was not a common complication. In only 3 of the 15 patients who had their ileostomy primarily for severe bleeding was the bleeding controlled by the ileostomy alone. In the remaining 12 an additional surgical procedure, partial or even complete colectomy, was required to stop profuse rectal hemorrhage. There were 10 patients in whom extensive regional ileitis developed that was of sufficient severity to require operative intervention in addition to ileostomy and colectomy.

Ten patients became pregnant after their ileostomy. In the five patients in whom pregnancy complications developed, a part or all of the colon remained. If possible, therefore, pregnancy should be postponed until after colectomy has been carried out. Carcinoma of the colon developed in 11 patients (3.5%). The incidence of carcinoma was high in patients in whom colitis had persisted for eight years or more. Recurrence of ulcerative colitis presents a serious hazard. While it seems reasonable to treat ulcerative colitis that is limited to the ascending colon by right colectomy, with immediate restoration of intestinal continuity, it must be kept in mind that this procedure has been associated with a high incidence of recurrence owing to the fact that it is difficult to determine how far the disease actually extends. For the same reason a colostomy has proved unsatisfactory even for those patients with disease apparently limited to the distal colon and rectum.

Aerosols in Surgery: Contribution to Prophylaxis and Therapy of Complications of Air Passages. A. Schmitt. Medizinische, No. 7, pp. 249-253 (Feb. 18) 1956 (In German) [Stuttgart, Germany].

Observations made by the author on patients who underwent operations on the cranium and brain, neck, thorax, or abdomen at the surgical clinics of the University of Mainz, Germany, and of Homburg, Saar, showed that the use of general aerosols in the preoperative phase may effectively combat infections of the air passages, produce improvement of asthmatic and asthma-like conditions, and, when combined with preparatory respiratory exercises, create a favorable pulmonary condition for the surgical intervention and for the postoperative course. Antibiotic aerosols and aerosols that exert a specific effect on the bronchi were used. The advantage of inhalation of antibiotics such as penicillin, streptomycin, tyrothricin, chlortetracycline (Aureomycin) and oxytetracycline (Terramycin) consists in the fact that the antibiotic in high concentration can be carried to the pulmonary focus and may even exert its action when parenteral administration of antibiotics is ineffective.

Practiced postoperatively, antibiotic aerosol treatment combined with inhalation of broncholytic drugs relieves respiratory difficulty and is a reliable prophylactic against postoperative bronchitis and pneumonia. Determinations of resistance of causative agents to the antibiotics are desirable. Postoperative prophylaxis of bronchopulmonary complications may be carried out most effectively when aerosol treatment is combined with adequate parenteral administration of respiratory stimulants, antibiotics and bacteriostatics, and with the use of oxygen and respiratory exercises. A scheme of the indications of aerosols in surgery is presented that includes surgical diseases associated with circulatory risk and respiratory difficulty such as severe infectious diseases, cachexia, thoracic injuries, as well as chronic diseases and postoperative complications of air passages, such as tracheal irritation, mild and severe (infectious) catarrhal conditions, asthmatic conditions, emphysema, congestive bronchitis, bronchiectasis, atelectasis, pulmonary infarcts, and pneumonia.

GYNECOLOGY & OBSTETRICS

Brenner Tumours of the Ovary: A Report of Nine Cases Including One with Malignant Degeneration. C. J. Mackinlay. J. Obst. & Gynaec. Brit. Emp. **63:**58-67 (Feb.) 1956 [London, England].

Mackinlay presents observations on nine patients with Brenner tumors removed at a Glasgow hospital in the 24-year period ending in 1954. In seven cases the patient was operated on for ovarian disease, and in two cases the Brenner tumor was found as a result of routine pathological examination. The hospital is devoted solely to the treatment of gynecologic conditions, and during the 24 years over 75,000 patients were admitted and 1,491 ovarian neoplasms were removed. Thus in this series Brenner tumors formed about 0.6% of all ovarian neoplasms. The oldest patient was 64 and the youngest 42 years; the average age of patients on discovery of Brenner tumors did not materially differ from that of patients with other solid tumors.

Brenner tumors are closely related to pseudomucinous cysts. They are classified in a special group because of histological peculiarities. For descriptive purposes, Brenner tumors may be divided into three types. The commonest in this series is the type that appears as a solid growth in the wall of a pseudomucinous cyst. Such a tumor shows the whorled appearance of the cut surface indistinguishable to the naked eye from a fibroma. The second type is the solid tumor large enough to be felt on bimanual examination. The third type is that which is found on pathological examination and is so small that the examiner may not be aware of its existence. The author dis-

cusses the possibility that the epithelial cords may arise from the ovarian stroma by metaplasia. Abnormal uterine bleeding may be associated with the Brenner tumor. The possibility that some Brenner tumors may secrete an estrogenic hormone cannot be altogether disregarded. The epithelial columns of the Brenner tumor may become malignant.

Prolonged First Stage of Labour. J. Sturrock and R. Brown. J. Obst. & Gynaec. Brit. Emp. **63**:83-86 (Feb.) 1956 [London, England].

In the decade 1940-1949, out of a total of 124 maternal deaths in the Simpson Memorial Maternity Pavilion in Edinburgh, 31 were in patients who had been in labor over 30 hours. Of these, 26 were primigravidas and 5 multiparas. The main cause of death was sepsis in 13 cases; post-partum shock and hemorrhage in 10, rupture of the uterus in 3, pulmonary embolism in 2, and hepatic toxemia in 3 cases. Since 1944 there has been only one death from sepsis in women with prolonged labor. Post-partum shock is now the chief cause of death in prolonged labor. In order to assess maternal morbidity and fetal losses the authors analyzed all cases in the years 1940 and 1941 and in the years 1948 and 1949 in which labor lasted over 30 hours. They conclude that maternal mortality in prolonged labor has been greatly reduced. Maternal morbidity in cases of prolonged labor, in spite of the use of antibiotics, was five times as high as the general morbidity rate. The total fetal loss in cases of prolonged labor in 1948 and 1949 was 9.5%, which was only a 3% improvement over the loss in 1940-1941. In nearly half the cases of prolonged labor relative disproportion was found to be present. Better recognition of contracted pelvis is attributed to a more general use of x-ray pelvimetry, which permits of a study of pelvic architecture as well as measurement of diameters.

Much improvement is still required in the management of relative disproportion due to a large baby and in cases of malpresentation and malposition where the labor is prolonged. More accurate appreciation of fetal anoxia in its earlier stages is necessary. Intact membranes are not necessarily a fetal safeguard. Artificial rupture of the membranes in prolonged labor and gentle easing of the head on each vaginal examination, when assessing progress, may show meconium to be present long before changes are recognized in the fetal heart rate. The authors advise more frequent resort to cesarean section in cases of prolonged labor in the interests of the child. Even if the cervix eventually dilates, the child by then is less able to withstand a vaginal delivery. The fetal loss in multiparas was much higher than in primigravidas where labor was prolonged. This may be due to the less frequent occurrence of disordered uterine action in multiparas and the greater likelihood of the delay being due to a relative disproportion. The authors advise earlier resort to cesarean section in primigravidas over 30 years of age in whom relative disproportion exists. Once progress, as indicated by progressive dilatation of the cervix, stops in labor over a period of 8 to 12 hours, delivery should no longer be delayed, because there is practically no hope that progress will again occur.

The Value of Antenatal Exercises. C. W. F. Burnett. J. Obst. & Gynaec. Brit. Emp. **63**:40-57 (Feb.) 1956 [London, England].

Although much time and energy are being devoted to antenatal physiotherapy throughout Britain, its true value is unknown. Obstetricians have tried to clarify the effect of exercises on (1) the duration of labor and the incidence of complications and (2) the amount of pain experienced. This paper is an attempt to clarify the first of these issues by reporting on studies at two maternity hospitals. Relaxation and exercise classes were held twice a week, special attention being devoted to correct breathing, relaxation, and exercise of the muscles used during the second stage of labor. The assumption of postures adopted during delivery is also practiced so that they will not appear strange to the patients when they are in labor. Time is given to psychological training, and while the discomforts of labor and the need for hard physical work are not minimized, every means is taken of banishing fear and giving the patients confidence in both themselves and their attendants.

An analysis of 2,675 cases shows that, despite much painstaking work on the part of doctors, midwives, and physiotherapists, antenatal relaxation and exercises have no influence on the length and character of labor. Not only do the duration of labor and the incidence of complications differ but little in the exercised and unexercised groups of patients, but the differences show no consistent trend, sometimes being in favor of exercises and sometimes against them. The patients are not very enthusiastic in attending classes; in spite of persuasion they appeal to only 20% of primigravidas and 3% of multiparas. The investigation is not a controlled experiment. Although they have no effect on the character of labor, antenatal exercises may be beneficial in other ways. It is generally agreed that postnatal exercises are performed more efficiently by the patient who has exercised during pregnancy, and it is often maintained by midwives that the mother who has practiced relaxation is better able to breast-feed her baby and to cope with her household duties when she returns home. As many of these benefits result from psychological causes, it is possible that it is psychotherapy that is of real value. The author believes that antenatal preparation for labor lies in the forging of a relationship between the patient and her attendant rather than in holding large classes for the practice of relaxation and exercises. Education and reassurance should be given antenatally, but the instruction should be personal and the teacher should be present during labor to encourage the patient and to enforce the teaching. Delivery is a specific achievement of the patient and her attendant rather than a mass production by a staff of supervisors lecturing to classes of expectant mothers.

Toxemia of Pregnancy as Seen by an Internist: An Analysis of 1,081 Patients. F. A. Finnerty Jr. Ann. Int. Med. **44**:358-375 (Feb.) 1956 [Lancaster, Pa.].

A toxemia clinic was instituted at the District of Columbia General Hospital in July, 1952. Since the analysis of the first 303 cases, published in 1954, some ideas on classification have changed. A total of 1,081 patients has now been studied, and some have been followed up for three years. The author gained the impression that hypertensive vascular disease and pyelonephritis frequently masquerade as toxemia of pregnancy. The triad of an elevated blood pressure, edema, and albuminuria or any one of these three signs has been seen in each of these diseases. Experience has shown that ophthalmoscopic examination and a complete urinalysis permit differentiation of these diseases.

Toxemia exists when the ophthalmoscopic examination reveals a retinal sheen and normal arteries and urinalysis reveals only albuminuria. Hypertensive vascular disease exists when the retinal arteries show hypertensive changes and no retinal sheen is present. When both hypertensive changes and a retinal sheen are seen on ophthalmoscopic examination, with or without albuminuria, toxemia is then superimposed on hypertensive vascular disease. The finding of normal fundi and albuminuria suggests pyelonephritis; clumps of white blood cells and glitter cells document the diagnosis. Though a retinal sheen and albuminuria are seen in both toxemia and acute glomerulonephritis, microscopic hematuria (occasionally gross hematuria) is seen more commonly in glomerulonephritis. Though 95% of the patients referred to the clinic were originally diagnosed as having toxemia, only 13% had toxemia by the criteria established in these studies. The diagnoses included hypertensive vascular disease in 666 patients, hypertensive vascular disease plus superimposed toxemia in 90, postpartum hypertension in 72, pure toxemia in 154, pyelonephritis in 56, edema without disease in 38, and unrelated cardiac or renal disease in five. The ability to differentiate the various disease states provided an opportunity to investigate whether toxemia caused vascular damage. One hundred twenty-five of the 154 patients with pure toxemia revealed no abnormality six weeks after delivery. In the other 29 women, however, despite return of the blood pressure to normal and disappearance of edema and albuminuria, examination of the retina revealed definite retinopathy. These retinal changes are attributed to the duration of the toxemia rather than to its severity.

PEDIATRICS

Nonerythroblastotic Kernicterus of the Newborn: Acute Forms and Sequelae. R. Sacrez, J.-G. Juif, L. Fruhling and others. Semaine hôp. Paris **32:**596-604 (Feb. 20) 1956 (In French) [Paris, France].

Jaundice of the newborn without blood incompatibility is not rare, but it is chiefly limited to premature and debilitated babies. The authors saw 14 such cases in four years. The first symptoms appeared between the fifth and seventh days of life. Those of cerebral involvement were severe, and there were also more specific signs such as hypertonia and athetoid movements. Death is the most frequent outcome of this acute stage of the disease. Some authors have reported the mortality to be 100%; eight patients of the present series died, usually within 48 hours after the onset of symptoms. The surviving babies have severe sequelae: five of this series had an extrapyramidal syndrome and the sixth considerable mental deficiency. The pathogenesis of nonerythroblastotic kernicterus is postulated to be the following: The premature infant develops an infection and thereby increases his hyperbilirubinemia. The infection is really the expression of metabolic disorders that severely affect the nerve cells, which are already influenced by anoxia. Then the grey matter becomes impregnated with bile. It might be worthwhile to practice routine checking of the amount of bilirubin in all premature babies and to perform exchange transfusion in those whose bilirubin values are excessively elevated.

Prevention of Recurrent Rheumatic Fever: The Use of Repository Benzathine Penicillin G. A. M. Diehl, T. R. Hamilton and J. S. May. South. M. J. **49:**250-259 (March) 1956 [Birmingham, Ala.].

According to a program initiated in February, 1953, at the Children's Convalescent Center in Kansas City, Mo., in an attempt to prevent streptococcic disease in rheumatic patients, 118 children with rheumatic fever were given 1,200,000 units of benzathine penicillin G intramuscularly every 28 days for periods varying from 6 to 32 months. The average age of the patients was 12 years. Seventy-six of the 118 children were girls and 42 were boys. Of 2,817 nose and throat cultures for beta hemolytic streptococci secured from these patients, 2,738 were taken after the initiation of prophylaxis. Of the 49 positive cultures for beta hemolytic streptococci, only 13 were proved to be of Lancefield group A type. After base line antistreptolysin O titers had been established, significant rises were observed in only four cases; none of these was preceded by a positive culture. Of 3,041 injections of 1,200,000 units of benzathine penicillin G (an average of 25.8 injections per patient), none caused serious local or systemic toxic reactions in these children. No episodes of recurrent rheumatic fever occurred. These data support Stollerman's observation of the efficacy of the administration of 1,200,000 units of benzathine penicillin G every 28 days in preventing further attacks of rheumatic fever.

Until more is known about the pathogenesis of rheumatic fever, the present logical approach toward prevention is aimed at prompt and adequate therapy of acute streptococcic infections and the use of a continuous prophylactic agent in persons who have had one or more attacks of rheumatic fever. Penicillin is presently the drug of choice. Intramuscular administration of 1,200,000 units of benzathine penicillin G every 28 days is the surest and frequently the most practical prophylactic method of preventing recurrences of rheumatic fever.

Clinical and Anatomic Study of a Case of Hand-Schüller-Christian Disease in a Child Followed for Three Years. J. Chaptal, P. Cazal, R. Jean and others. Semaine hôp. Paris **32:**589-596 (Feb. 20) 1956 (In French) [Paris, France].

A boy was hospitalized at the age of three years and four months for cachexia and diabetes insipidus of two months' duration. He was extremely pale, with a large skull (perimeter 49 cm.), bilateral exophthalmos, enlargement of the liver and spleen, and papulous and purpuric lesions of the skin and oral mucosa. He was voiding from one to three liters of urine a day. Cranial palpation showed a gap two by three centimeters in area in the left occipital region. Radiography showed destruction of the sella turcica. The patient was moderately anemic, with a lymphoblastic reaction in both serum and bone marrow. There was, however, neither hyperlipemia nor hypercholesteremia. The patient's condition was improved by irradiation of the cranial dome, but this therapy did not prevent an increase in number and size of the cranial separations. He deteriorated progressively despite a second course of roentgen therapy to the skull and treatments with radioactive phosphorus, antidiuretic hormone, and cortisone (for an aplasia of the bone marrow occurring late and independently of the leukoblastic reaction, which had regressed). Deafness supervened a year after the first admission. The patient died two years and five months after the first admission.

The case of this boy differs from other reported cases of Hand-Schüller-Christian syndrome in which remissions were obtained after radiotherapy in that there was a dissociation between the arrest of progression with disappearance of the diffuse lesions and the continuing development of the cranial lesions. Throughout the period of observation the hepatosplenomegaly persisted, but repeated punch biopsy showed no abnormalities other than moderate reticular hyperplasia and mononuclear infiltration of the liver. The postmortem histological studies revealed intensive reticuloendothelial reaction to be a dominant characteristic of the disease. In this patient, the reaction was seen in both its nonspecific and specific aspects: there was simple hyperplasia in the liver, spleen, and lymph nodes and a variety of abnormal cells, including pigment-containing histiocytes, giant cells, multinucleated cells, and foam cells (arising from hypertrophied histiocytes that undergo vacuolization). Hand-Schüller-Christian disease can be defined as a hyperplasia of the reticuloendothelial system that manifests itself in pseudotumoral form and progresses toward a reticulosis and, eventually, to fibrosis.

The Rheumatoid Form of Infantile Leukemia. P. Fornara. Minerva pediat. **7:**1624-1629 (Dec. 15) 1955 (In Italian) [Turin, Italy].

Little is known about those forms of infantile leukemia the onsets of which are characterized by frank rheumatic symptoms, often leading to wrong diagnosis. The author cites histories of three children in whom the diagnosis of rheumatoid subacute leukemia was made on the basis of the roentgenograms, the findings in the bone marrow, and biopsy of the lymph nodes or other tissue. The duration of the condition was long, and fever had an undulant course. The joint manifestations were accompanied by a pseudoinflammatory involvement, which extended to the skin. Mikulicz's disease was often present concurrently. The blood findings were those of anemia with constant leukopenia. Despite blood transfusions and antibiotic, sulfonamide, and salicylate therapy, the three children died. Fornara believes that the rheumatoid symptoms of acute infantile leukemia can be attributed to the reticuloendothelial proliferative action from which the leukemia itself originates. Another Italian author, Belloni, states that the skeletal alterations that occur in the course of leukemia are the expression of stimulation of the mesenchyma by the proliferated leukemic cells.

Experiences with Surgical Treatment of Hirschsprung's Disease. F. Rehbein and H.-H. Wernicke. Beitr. klin. Chir. **191:**18-34 (No. 1) 1955 (In German) [Munich, Germany].

Thirty-one children, 27 boys and 4 girls between the ages of 6 months and 14 years, with congenital megacolon (Hirschsprung's disease) were operated on at the surgical department of the pediatric clinic in Bremen, Germany. The "narrow segment," the portion of the colon with aplasia of the intramural ganglion cells of Auerbach's and Meissner's plexus, was demonstrated by preoperative roentgenologic examination in every one of these patients. It could be clearly delimited from the proximal dilated portion of the colon in most of the patients. Rectosigmoidectomy, according to Swenson's technique, was performed on 17 patients. Resection was done proximally in the dilated portion of the colon several centimeters above the narrow segment and 1 to 2 cm. distally above the anus. Follow-up of these 17

patients varied from 18 months to four years. Results were satisfactory in 12 patients. Enemas or administration of drugs were still required because of constipation in three patients. Two infants died. Postoperative sphincter incontinence occurred but subsided almost completely, although occasionally only after several months. Disturbed micturition, a sign of injury to the innervation of the bladder caused by the surgical intervention, was observed but also became normal again. A cure may be obtained with great probability by the resection of the narrow segment including the rectum. In 13 patients the rectum was preserved and the narrow segment removed together with the major portion of the dilated colon. Hochenegg's pull-through technique was used in two of these patients, while an intra-abdominal anastomosis was performed in the remaining 11. Thereafter dilatation of the sphincter was carried out. The results obtained by this method, which has been recommended by State in THE JOURNAL (**149:**350 [May 24] 1952), were equally good. The preservation of the rectum appears advantageous because damage to the vegetative fibers in the pararectal area can thus be avoided.

DERMATOLOGY

Acneform Eruption Due to Corticotropin. M. Sullivan and I. Zeligman. A. M. A. Arch. Dermat. **73:**133-141 (Feb.) 1956 [Chicago].

In some patients receiving corticotropin there develops an eruption that resembles acne vulgaris in many respects. Biopsy specimens were taken from early and advanced lesions of 6 patients exhibiting acneform eruptions due to corticotropin and from similar lesions of 15 patients with acne vulgaris. Microscopic studies revealed similarities in the development of the two conditions. The primary alteration is hyperkeratinization of the follicular orifice. This is followed by the formation of an epithelial cyst. Later, there is a perifollicular cellular infiltration that is followed, in some cases, by a foreign-body type of granulation tissue and suppuration. There are also differential histological features. The lesion of acne vulgaris is larger than that of the drug eruption. Abscess formation is more frequent and more extensive in acne vulgaris. Perhaps the most important difference is the normal appearance of the sebaceous glands in the corticotropin eruption as contrasted with the hyperplasia in acne vulgaris. The authors believe that the dual origin of acne vulgaris, namely, influence of the adrenal cortex plus the ratio of androgens and/or progesterone to estrogens, contrasted with the single origin of the acneform eruption, namely, influence of the adrenal cortex, may account for the distinguishing gross and microscopic findings.

The Use of Soap and Detergents in Skin Diseases: An Evaluation of a New "Soapless Soap." L. D. Grayson. Am. Pract. and Digest Treat. **7:**269-272 (Feb.) 1956 [Philadelphia].

A new antiseptic "soapless soap" called Lanolin-Foam, an amionic (alkyl aryl sulfonate) detergent bar containing 8% lanolin, 2% bithionol (2,2'-thiobis [4,6-dichlorophenol]), and utilizing mineral and other waxes as a binder, was used in 54 patients with various dermatoses and 5 normal persons. This new detergent bar dissolves in water, forming a solution with a pH of 6.9, and is used in a cellulose sponge that causes aeration of the soapy solution and thus forms a foamy lather that facilitates cleansing. The dermatoses for which it was used included such conditions as acne vulgaris, furunculosis, miliaria rubra, hidradenitis, and seborrhea, in which the use of soap and water was indicated, and other conditions such as atopic and contact dermatitis, tinea, nummular eczema, pityriasis rosea, and exfoliative dermatitis, in which water and soap are usually avoided. Forty-five patients with 20 different dermatoses and the five normal persons (more than 90% of those using the product) were satisfied with the result. Five patients were lost to follow-up. In only one patient (with acne) burning and redness was caused either by irritation or by sensitivity. Two other patients with acne had flare-ups, and in a 16-month-old child with atopic dermatitis a rather severe impetigo developed 17 days after use of the sponge soap was started. Simple cleansing with non-irritating agents is in itself a very useful treatment in many lesions of the skin.

OTOLARYNGOLOGY

A Bacteriologic Investigation of Otitis Media in Infancy. E. A. Mortimer Jr. and R. L. Watterson Jr. Pediatrics **17:**359-367 (March) 1956 [Springfield, Ill.].

Cultures of middle ear exudates obtained from 104 infants aged less than 2 years with clinical otitis media showed that the chief bacterial causes of this condition in infancy are pneumococci and Hemophilus influenzae. Beta hemolytic streptococci were also found, but only in two cases. Material for examination was withdrawn from the middle ear by aspiration through the drum. Experience in the first few cases showed that contamination from the external surface of the drum could not be avoided, and thereafter aspiration was invariably preceded by the culturing of material procured by a cotton swab from the external drum surface in an effort to differentiate the actual middle ear flora from the contaminating external organisms. No middle ear exudate was obtained from 36 of the 104 patients, either grossly or on smear, and external cultures were sterile. Micrococci (staphylococci), diphtheroids, and occasional miscellaneous organisms were frequently isolated from middle ear cultures in the 68 cases in which purulent matter was obtained, but they were believed to be contaminants. Organisms regarded as causative, that is, pneumococci, beta hemolytic streptococci, and H. influenzae, on the other hand, were never isolated from the external cultures, except on one occasion when a Hemophilus was obtained from an ear in which perforation had apparently just occurred. The cultures proved to be inexplicably sterile in 25 cases, in 12 of which the matter obtained was purulent, as shown by the smears. One of the 25 patients was subsequently found to have received antibiotics several days previously, but attempts to account for the discrepancy between the cultures and the smears were generally unsatisfactory. Investigation of the nose and throat flora resulted in the isolation of two or more potential pathogens from the upper respiratory tract of most (70%) of the patients.

Nasopharyngeal and pharyngeal cultures, however, are of little value in the determination of the bacterial origin of otitis media, more because the presence of too many potential pathogens creates confusion than because the offending organism is absent. The only accurate inference that can be drawn from a correlation of these cultures with those from the middle ear is that an organism not found in the nose or throat is not likely to be found in the middle ear. Most of the patients had upper respiratory tract disease, some had probable bronchopneumonia, and at least one had exanthema subitum (roseola infantum). The frequency with which H. influenzae was isolated from the middle ear suggests that antimicrobial drugs such as penicillin that are effective primarily in gram-positive infections are not adequate in the treatment of otitis media in infancy.

Topical Use of Prednisolone in Nasal Allergy: Report of a Controlled Study. J. R. Anderson and H. D. Ogden. Ann. Allergy **14:**44-46 (Jan.-Feb.) 1956 [St. Paul].

The authors investigated the intranasal use of prednisolone. Thirty patients with nasal allergy were selected from those attending the Allergy Clinic of the New Orleans Eye, Ear, Nose and Throat Hospital. Aside from the physical manifestations of nasal allergy, all had a positive family history, positive nasal eosinophilia, confirmatory skin tests, and history of allergy in childhood. Three separate solutions were used; these were labeled A, C, and D and were provided in plastic spray bottles. At the conclusion of the study, the manufacturer revealed that preparation A was the placebo, preparation C contained 0.5 mg. of prednisolone per cubic centimeter (a 0.05% solution), and preparation D contained 1 mg. of the steroid per cubic centimeter (a 0.1% solution). Each patient received each preparation for a period of one week. Between treatment periods, a rest interval of one week was inserted in order to avoid any carry-over effect from the previous preparation. The results of a nasal and cyto-

logical examination were recorded prior to dispensing each preparation; at the end of the week these were repeated and the results were compared.

None of the patients who received solution A (the placebo) showed any clear-cut subjective or objective improvement as compared to the improvement with the other two solutions. All patients reported varying degrees of subjective improvement after using solutions C and D. Twenty-four patients stated that they obtained more subjective improvement after using C than after using D; this was confirmed by examination of the nose. Most of these individuals were people whose nasal allergy was not accompanied by a great deal of metaplastic change in the nasal mucosa. Six of the patients reported greater subjective improvement with solution D than with solution C; this was also confirmed by examination of the nose. The nasal allergy in these patients was farther advanced, so that the mucosa showed more metaplastic changes, or they had been submitted to previous surgery that interfered with normal nasal physiology. Careful selection of cases and initial saturation of the nasal tissues is necessary in order to obtain good results with this, or any other, type of topical steroid therapy in the nose.

Hematotympanum at Reduced Barometric Pressure. D. A. Vavala. U. S. Armed Forces M. J. **7**:436-438 (March) 1956 [Washington, D. C.].

Hematotympanum developed in an aviation cadet who, together with 15 other students, was subjected to a routine type 2 chamber flight. This flight involves "ascent" from ground level to a simulated altitude of 43,000 ft. and "descent" to ground level. Ascent and descent are made at a rate of 2,000 ft. per minute. The cadet had never previously experienced any unusual symptoms at altitude, and was free of upper respiratory infections, headaches, and diarrhea. He had received no immunizations within the past 14 days, was not fatigued, and had had more than six hours' sleep the night before. The chamber reached the simulated altitude of 43,000 ft., leveled off for about two minutes, and then made a free fall to 30,000 ft. The chamber was leveled off at this altitude long enough to ascertain if anyone was having difficulty clearing his ears. Since no one was experiencing any difficulty, the chamber resumed its descent to ground level at the rate of 2,000 ft. per minute. At 18,000 ft., the cadet signaled that his ears were blocked. The chamber was immediately leveled to allow him to clear his ears, which he accomplished without difficulty. He experienced no pain, merely a sensation of fullness. The chamber resumed its descent. At 5,000 ft. the observer noticed blood oozing from the cadet's left ear.

After ground level was reached examination revealed that the outer cutaneous layer of the tympanum on the left side had become separated from the rest of the ear drum. There was fresh blood on the ear drum and in the external canal. No pain was present in either ear. The bleeding was stopped and therapy against secondary infection instituted. The ear drum healed completely without any impairment of hearing. Possible causes of the development of the hematotympanum are discussed, and traumatic rupture incidental to reduced barometric pressure is regarded as the most likely cause.

Reaction to Cocaine Used as Topical Anesthetic in Bronchoscopy: Study of One Thousand Cases. R. A. Tella and W. Weisel. A. M. A. Arch. Otolaryng. **63**:115-119 (Feb.) 1956 [Chicago].

The authors review 1,000 consecutive bronchoscopies performed on 956 adult patients with the use of topical cocaine anesthesia. Seven minor and two severe anesthetic reactions occurred. The reaction to cocaine was of two main types: a minor or syncopal type of reaction and a severe or convulsive response. The reactions were similar to the untoward responses observed with tetracaine in a previous study. The incidence of toxic reactions was significantly lower in this series of patients with cocaine anesthesia than in the group in whom a 2% tetracaine solution was used. The authors gained the impression that whereas anesthesia with cocaine was adequate for endoscopy it was not so effective as that obtained with a 2% tetracaine solution in respect to duration of anesthesia and the abolition of the cough and gag reflex. The impression was corroborated by interviews with patients who were questioned subsequent to bronchoscopy after cocaine anesthesia, when previous endoscopy had been performed with the utilization of tetracaine. Although toxic reactions are less frequent with the use of cocaine than with tetracaine, the fact that reactions of a toxic nature do occur with cocaine makes it imperative that provision for management of these reactions be immediately available in the operating room. For that reason, endoscopy should be performed in a hospital where adequate preoperative medications can be utilized and where resuscitative measures are immediately available in the endoscopy room.

THERAPEUTICS

The Use of Metrazol in Non-Institutionalized Elderly Patients. E. H. Aschenbach. M. Ann. District of Columbia **25**:70-72 and 116 (Feb.) 1956 [Washington, D. C.].

The author began to use Metrazol in elderly patients in the hope of making these individuals more tractable in their own homes, thereby avoiding institutional care. The symptoms for which Metrazol was given were loss of memory, confusion, nervousness, suicidal tendencies, insomnia, fear of loss of mind, and loss of memory for surroundings, that is, beliefs of not being home and wandering off. The author began treatment with ¾ grain, given four times a day, and then gradually raised the dose; however, having seen no untoward reactions, he now starts treatment with 2 tablets given four times daily and raises or lowers the dose as he sees fit.

He presents the histories of 12 patients in whom he resorted to this treatment. He found that the drug is of value in certain cases of disturbed cerebral circulation, especially in patients in whom long-standing organic changes due to hypertension or arteriosclerosis are not present. A trial course of Metrazol is indicated in those troublesome cases in which such indications as memory loss might otherwise necessitate institutional care. Therapy with Metrazol in liquid form may improve dosage accuracy in those elderly individuals who lose or destroy the tablets or who are suspicious of being poisoned.

An Experimental Study of the Lethal Synergism Between Secobarbital and Alcohol. J. D. Archer. Texas Rep. Biol. & Med. **14**:1-5 (No. 1) 1956 [Galveston, Texas].

Officials of law enforcement agencies have long dealt with the increased severity of intoxication resulting from a combination of barbiturates and alcohol as contrasted with a similar dose of one drug alone. Clinical observers report a synergistic action in the lethal toxicity of the two drugs, but the question arises whether a potentiating synergism occurs between the drugs or only an additive synergism. The author describes experiments with secobarbital and ethyl alcohol carried out on adult mice. While these experiments confirmed the existence of a synergistic action between these two substances, they also indicated that apparently this synergism is additive instead of potentiating and probably involves slightly less than a total summation of the theoretically expected toxic actions of the two drugs.

It should be emphasized that a failure to show a routine and predictable potentiating action between barbiturates and alcohol in laboratory animals by no means rules out the possibility of such an action. Deaths from such a phenomenon apparently do occur in an occasional susceptible individual. The rapidity of some such deaths as contrasted with the usual deaths from barbiturates or alcohol alone further emphasizes the fact that in a susceptible person, the toxicity of a combination of the drugs may be greater than could be explained from a simple summation of the expected effects of each drug.

Selective Irradiation of Lymph Nodes by Interstitial Injection of Radioactive Colloidal Gold. H. F. Berg and W. M. Christopherson. Am. Surgeon **22**:172-178 (Feb.) 1956 [Baltimore].

A colloidal solution of radioactive gold (Au^{198}) of particle sizes ranging from 0.003 to 0.004μ was injected interstitially into various organs or tissues of dogs such as the submucosa of the

right intermediate bronchus and the superior mammary gland. Microscopic sections and autoradiograms were made of the regional lymph nodes, and some 600 separate lymph nodes were examined in this manner. The time interval from the injection of the colloidal radioactive gold to the examination of the lymph nodes varied from one hour to 25 weeks. The dose of isotope used varied from 2 mc. to 100 mc. Fractional injections were compared to single injections, and the effect of blocking the afferent lymphatics on subsequent irradiation was studied.

Results showed that when colloidal Au^{198} is injected interstitially, the radioactive particles are mobilized and are concentrated in the regional lymph nodes. The colloid is present in appreciable amounts in the nodes within three hours after intramammary or intrabronchial injection. This is well within the half-life of the isotope, which is 2.7 days. Radiation changes of varying degrees can be produced within the lymph nodes. The extent of the change is dependent on the proximity of the nodes to the injection site and the amount of isotope injected. The tolerance level of the injection site restricts the amount of Au^{198} that can be used to effect radiation necrosis of the node. The tolerance varies from organ to organ and probably is dependent to some extent on the rapidity and completeness of mobilization. There is no appreciable dissemination of the isotope to other organs of the body, and no untoward effects have been found in the liver, spleen, or bone marrow. The affinity that lymph nodes have for Au^{198} when it is injected in this manner offers an additional method for delivering ionizing radiations. The failure to obtain an even distribution of the colloid in all nodes draining a given area and the probability that metastatic cancer would obstruct some of the afferent lymphatics and thus prevent effective irradiation of the lymph nodes are factors that might limit the clinical success of this type of therapy.

PATHOLOGY

Arteriosclerosis in the Intramural and Extramural Portions of Coronary Arteries in the Human Heart. J. C. Edwards, C. Burnsides, R. L. Swarm and A. I. Lansing. Circulation **13:**235-241 (Feb.) 1956 [New York].

Fifteen instances of intramural coronary arteries were observed in the dissection of 276 human hearts at consecutive unselected autopsies. All or a major portion of a coronary artery was covered entirely by myocardium. The incidence was of about one intramural coronary artery found among every 23 hearts examined. There were 13 left anterior descending coronary arteries, one right coronary artery, and one left circumflex coronary artery, all surrounded by myocardium for variable distances. In one instance, the right coronary artery had a main branch that ran intramurally. All other 14 intramural coronary arteries in the consecutive autopsies and one additional coronary artery, found in a heart not included in the consecutive group of autopsies, were major coronary arteries. In none of the hearts was more than one intramural coronary artery found. Severe atheromas and narrowing of the lumens were observed in all but two of the intramural coronary arteries. Eight of the intramural coronary arteries had pronounced, six had moderate, and two had slight atherosclerotic changes. The other extramural coronary arteries in these hearts also showed atherosclerotic involvement. These findings suggest that the covering of a coronary artery in the human heart by myocardium during a part of its major course fails to protect it from the atherosclerotic process, which occurs there in much the same degree and is of the same type as in the extramural portions of the same arteries and in other entirely extramural coronary arteries.

Studies on Cancer of Lung: 6. Relation between Cancer of Lung and Tobacco Smoking in Norway. L. Kreyberg. Tidsskr. norske laegefor. **76:**67-72 (Feb. 1) 1956 (In Norwegian) [Oslo, Norway].

The relation of tobacco smoking to the development of primary malignant pulmonary tumors was investigated in Norway. The material consisted of 300 cases, in 258 men and 42 women, registered from 1951 to 1955. The occurrence of group 2 tumors in men and women shows no relation to tobacco smoking. About four out of five cases of group 1 tumors in Norway today are related to tobacco smoking; the relation is especially marked when cigarettes are used, exclusively or in part, and the relation is certain though less marked in those who smoke only pipes. Increasing use of tobacco is accompanied by increasing risk. Other possible carcinogenic factors should not be ignored. There is no evidence that general pollution of the air may be significant, but work in dusty air may play a part.

The possibility that men are predisposed to develop group 1 tumors cannot be disregarded. Wheather this predisposition results from different macroscopic architecture of the lungs, a different biological response from the epithelium, or from hormonal factors is unknown. While group 2 tumors occur with approximately the same frequency in men and in women, in town and country, and independently of tobacco smoking, group 1 tumors show a far greater relative frequency in men than in women, in nonsmokers as well as in smokers. About 90% of the primary epithelial tumors of the lung in women are of the group 2 type. The effects, in terms of increased incidence of pulmonary tumors, of the changes in the smoking habits of women in recent years cannot be expected to register to any extent for several decades. In men, group 2 tumors constitute less than 20% of all primary epithelial tumors of the lung. Since these and about one-fifth of group 1 tumors are not related to tobacco smoking, the conclusion is that about one-third of all primary tumors of the lung in men today show no relation to tobacco smoking and about two-thirds do show such a relation. The latter fraction is steadily increasing. The figures reported in this study are regarded as a generally valid expression of the present situation in Norway.

Calcification of Regional Lymph Nodes Following BCG Vaccination. S. C. Stein and M. J. Sokoloff. Am. Rev. Tuberc. **73:** 239-245 (Feb.) 1956 [New York].

Roentgenograms of the chest and axilla obtained in 34 white and 471 Negro infants who had received an intracutaneous injection of BCG vaccine shortly after birth were studied to determine whether calcification of the nodes draining the site of BCG vaccination occurs and whether it is related to the swelling or suppuration of these nodes. The roentgenographic examination was made from 1 to 54 months after vaccination, and shadows, either single or multiple, with the density of bone were interpreted as calcium. Healed calcific axillary nodes were found in a significantly higher percentage of white than of Negro infants. The precise time at which calcification of the nodes occurred is not known, because the roentgenographic examinations were not made at repeated stated intervals; in one Negro infant, however, it was present as early as two months after vaccination. The percentage of infants showing calcification of the axillary nodes rose sharply in the group that had been vaccinated from 7 to 12 months before roentgenographic examination and remained relatively constant thereafter, suggesting that calcification probably occurred within one year after vaccination in most cases.

The fact that calcium is usually deposited in chronically inflamed areas where necrotic material, especially tuberculous material, has not been completely removed or absorbed, led to a correlation of calcification with the postvaccinal condition of the axillary nodes. Calcification was found in a higher percentage of white than of Negro infants without visible or palpable enlargement of the axillary nodes. The occurrence of calcification, on the other hand, was more frequent in the Negro infants who showed either swelling or suppuration of the nodes than in those in whom the nodes remained grossly unchanged. The somewhat less frequent occurrence of calcification noted among those whose lymph nodes had suppurated than among those whose nodes were swollen but did not suppurate may be due to the fact that the necrotic material had been constantly eliminated from the suppurating nodes by drainage. The suggestion has been made that, when liquefaction takes place within the necrotic material before calcification sets in, there must first be an absorption of the fluid, then an inspissation of the necrotic contents, and then a deposition of calcium salts in the necrotic material, and that the occurrence of calcification is delayed by this process.

BOOK REVIEWS

Clinical Studies in Neurology. By Harry Lee Parker, M.S., M.D., F.R.C.P.I., Professor of Neurology, Mayo Foundation, Graduate School, University of Minnesota, Rochester. Cloth. $6.50. Pp. 364. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada. 1956.

This is an unusual book for today's student of neurology. The author had a rare teaching experience and has faithfully recorded his lectures over 12 years on diseases of the nervous system at his parent university, Trinity College, Dublin, Ireland. These lectures appear just as they were recorded, except for a few additions to bring them up-to-date. The style is informal, witty, and interspersed with historical allusions and local color, but it is deeply imbued with scholarly and scientific evaluation and discussion of the more common neurological conditions found in the wards of any large municipal hospital. This form of clinical lecture has almost disappeared from medical literature. To revive it is courageous and in this instance worthwhile. Today's student can read this book with pleasure, catch the spirit of the author, and visualize his patients as he presented them in his characteristic, enthusiastic manner. He stresses the difficulties of clinical teaching, the importance of treating patients humanely and as equals, and finally the value of kindness to both patients and fellow craftsmen. Both students and teachers, therefore, may read this personal experience with profit.

Proceedings of the Underwater Physiology Symposium, January 10-11, 1955, Washington, D. C. Loyal G. Goff, editor. Prepared for Office of Naval Research, Washington, D. C., by Panel on Underwater Swimmers Committee on Undersea Warfare. Publication 377, National Academy of Sciences–National Research Council. Paper. $1.50. Pp. 153, with illustrations. National Academy of Sciences–National Research Council, 2101 Constitution Ave. N. W., Washington 25, D. C., 1955.

Enlivened by accounts of experiences of frogmen and limpeteers in World War II, this book deals with many topics of general scientific and special medical interest. An introductory section outlines the major problems of underwater swimming and self-contained diving. The next section is a seminar consisting of five contributions on oxygen toxicity; another consists of five contributions on decompression and the bends, bubble-formation, and the development of new mixtures, such as helium-oxygen, that have increased the depth to which divers can descend. The last section takes up other respiratory problems in diving, including the unexpected narcotic effects of argon and other noble gases when inhaled under pressure. The book contains much important information, many illuminating diagrams, and a valuable bibliography.

Integrated Gynecology: Principles and Practice. Volumes I, II and III. By I. C. Rubin, M.D., and Josef Novak, M.D., Professor of Obstetrics and Gynecology, University of Vienna. Cloth. $60. Pp. 589, with 218 illustrations; 496, with 164 illustrations; 682, with 129 illustrations. Blakiston Division, McGraw-Hill Book Company, Inc., 330 W. 42nd St., New York 36; 95 Farringdon St., London, E.C.4, England, 1956.

This book is published in three volumes with a total of more than 1,750 pages. It is well bound and is printed on glossy paper that takes the illustrations well. This remarkable book presents the personal observations of the authors. One can identify with at least some accuracy the portions to which each author has mainly contributed. Dr. Rubin presents the American viewpoint and Dr. Novak the European. There are many excellent photomicrographs, and the surgical techniques are adequately illustrated. At the end of each chapter there is a carefully selected bibliography. Each volume has its own adequate index. These books represent something between a textbook and a handbook. Some of the chapters, such as Dr. Rubin's chapter on infertility, are extraordinarily complete. The surgical techniques could be extended and such individual parts as the treatment of vulvar cancer could be improved. However, the book as it stands is the best available source among the English works and, as such, should find a place in the reference library of the occasional gynecologist and the specialist. The student will use it for reference as will the teacher. It is to be recommended without reservation for broad use.

Regeneration in the Central Nervous System by Thirty-Three Contributors. Edited by William F. Windle, Ph.D., Sc.D., Chief, Laboratory of Neuroanatomical Sciences, National Institute of Neurological Diseases and Blindness, Bethesda, Maryland. Foreword by Pearce Bailey, Ph.D., M.D., Director, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Md. Cloth. $9.50. Pp. 311, with 68 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1955.

Since the end of World War II, there has been a renewed interest in the problem of regeneration of nervous tissue within the central nervous system. One of the reasons for this reevaluation of an old problem is the survival of so many paraplegics who, despite the trauma to their spinal cords, have recovered from urinary infection, which was the common cause of death prior to the era of antibiotics. Previous studies have now been reassessed and much new work done on laboratory animals with improved techniques of suture and asepsis. There is much evidence for regeneration of the spinal cord in animals, and a number of convincing experiments are reported in this book. The condition in man, however, is less satisfactory, possibly because the nature of the trauma makes the operation more difficult than in animals. It is not easy to realign a broken, crushed spinal cord without setting up a large amount of intervening scar tissue. Reports claiming favorable functional regeneration in human spinal cords, moreover, have on reexamination been found to be extremely doubtful, even though the immediate results seemed promising. The subject of regeneration of the central nervous system received the attention of a group of investigators who met in May, 1954, in Bethesda, Md., at the invitation of the National Institute of Neurological Diseases and Blindness. The papers presented at that meeting are now available in this monograph. From them certain general conclusions can be drawn. The physiologists presented sound evidence that regeneration could take place in the central nervous system, and thus an idea firmly entrenched in neurological education for almost half a century must be set aside. This does not mean, however, that a simple demonstration of structural regeneration implies useful restitution of functions. What may be seen in man from the histological point of view is not perhaps quite as clear as that visualized in animals. There is enough evidence at hand, however, to justify continued research in this field, and the publication of the facts brought to light in the Bethesda symposium form a sound basis on which to start future investigations.

Strabismus: Diagnosis and Treatment. By Beulah Cushman, M.S., M.D., Attending Ophthalmologist, Passavant Memorial Hospital, Chicago. Cloth. $6. Pp. 208, with illustrations. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1956.

Dr. Cushman, after many years of study and practical application, has put into print in this small volume the teachings of Dr. Alexander Duane and his late illustrious assistant, Dr. James Watson White. As Dr. Vail so aptly states in his foreword, "the subject is far from being exhausted." However, Dr. Cushman's excellent review of all phases of the subject, her case history reports, and the fine illustrations of operative procedures make the volume one that goes far in the realization of the ideal presentation of the subject of strabismus. One criticism is that the use of abbreviations and signs might not be clear to the student. The book is highly recommended for all interested in oculomotor anomalies.

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

QUERIES AND MINOR NOTES

POLIOMYELITIS VACCINE WITHOUT PENICILLIN

To the Editor:—*A 17-year-old girl had an extremely severe reaction to penicillin at the age of 10. This reaction included exfoliative dermatitis of several weeks' duration and swelling of her joints for about three months. Can some poliomyelitis vaccine without penicillin included be obtained, and should this girl be given this?*

David L. Pressly, M.D., Statesville, N. C.

Answer.—The vaccine presently being produced by Wyeth laboratories has polymyxin substituted for penicillin. It is the feeling of the manufacturer, as well as others acquainted with the allergic reactions to penicillin, that this may be extremely valuable, particularly for those who cannot tolerate penicillin. While the vaccine, generally, is entirely free of antigens or other materials that might cause systemic reactions, it seems advisable in this particular case that, regardless of which manufacturer's vaccine is used, an intradermal skin test should be done prior to the administration of vaccine.

PRURITUS VULVAE

To the Editor:—*Please discuss the treatment, palliative or otherwise, of pruritus vulvae.* *M.D., Kansas.*

Answer.—The treatment of pruritus vulvae depends on the cause. In some cases the cause cannot be found or the etiological agent cannot be removed immediately, as, for example, the itching associated with pregnancy and that accompanying obesity. In these patients symptomatic treatment must be given at least for a while. Of greatest importance is cleanliness not only after each urination and bowel movement but at all times. In cleansing the vulvae there must be no rubbing, only patting, preferably with soft toilet paper, soft cotton, or soft tissue. One of the best suggestions is that the patient refrain from scratching no matter how great the urge. Scratching only aggravates the itching, and much greater relief can be obtained by pinching the portion of the skin that itches or by making firm continuous pressure on the involved parts with the closed fist or fingers. Hot applications may help, but again heat may aggravate the itching. Many women are relieved by the application of cold compresses. Lotions and salves containing phenol, sodium thiosulfate, and other substances are temporarily helpful. Various preparations may have to be tried. In every case of pruritus vulvae, it is essential to obtain a complete history and to make a thorough general and local examination. Regardless of the detection of an apparently local cause for the itching, the urine should always be examined for the presence of sugar. In some patients pruritus vulvae is the symptom that leads to the discovery of diabetes. Even if sugar is found in the urine, the vaginal secretion must be examined because in a large proportion of diabetic women who have pruritus of the vulva the cause of the itching is not the glycosuria but a monilial infection. Naturally women with diabetes must be treated for their diabetes as if there were no pruritus vulvae; such improvement benefits the local condition. If the itching of the vulva is due to the presence of Candida (Monilia), trichomonas, gonorrhea, the menopause, senile vaginitis, or kraurosis vulvae, these conditions must be treated. Pediculosis pubis occasionally causes pruritus. Treatment consists of removing the offending parasites, the Phthirus pubis, or crab louse, and the ova. When pruritus occurs in women past the menopause, hormone therapy usually gives relief. This may be in the form of preparations for oral use, such as diethylstilbestrol or other synthetic drugs, or natural estrogens given hypodermically. The doses are the same as for menopausal symptoms. Additional relief from the pruritus may be obtained by applying a salve containing estrogen to the vulva. In intractable cases of pruritus vulvae that do not respond to conservative measures, roentgen therapy has been tried but the results are most unsatisfactory. In some cases of intractable pruritus vulvae, relief can be obtained by the injection of alcohol or other substances, such as Zylcaine. The latter may be used as follows: Without shaving the pubic and vulvar hair the vulva is cleansed with green soap and washed with water. Four procaine wheals are made intracutaneously with a 27 gauge needle and syringe. The Zylcaine solution is injected along the length of both sides of the labia majora and minora, across and above the area of the clitoris, and across the lower portions of the vulva above the anal area. For each of the labia 5 to 10 cc. and for the supraclitoric and perineal body areas 2.5 to 5 cc. of the solution is used. For the injection a 21 gauge, 5 cm. (2 in.) needle or a spinal needle is introduced at the upper pole of the labia about 0.5 cm. away from the inflamed border and is carried down to the lower pole before the injection is begun. The solution is injected when the point of the needle is felt at the lower angle; after the injection in the lower pole the needle is withdrawn gradually upward depositing solution until the upper labial pole is reached. The injections are made fairly deep into the fleshy parts of the labia, but never should enough Zylcaine be injected to make the skin tense, or slough may result. Many patients obtain relief in one week, others in two weeks, and some not until later. Hydrocortisone, in the form of an ointment applied locally, relieves many women of pruritus vulvae.

ALLERGY TO SUNLIGHT

To the Editor:—*What is the treatment for an individual who is allergic to sunlight? Exposure to sunlight on all skin areas other than face or hands causes urticaria.*

Glenn E. Roark, M.D., Dierks, Ark.

Answer.—One of the most effective ways of preventing this type of hypersensitivity to sunlight is to cover the skin with an effective screening agent, such as a solution or ointment containing *p*-aminobenzoic acid. There are such preparations on the market. An effective ointment could be made up using an ointment base and placing a high concentration, say up to 5%, of the active principle in it. Another method would be the use of an antihistamine one-half to one hour before exposure to the sun. It is also possible that periods of short subclinical exposure to light, increasing the duration of exposure, may create a tolerance, in time, sufficient for normal purposes.

HEMORRHAGIC FLUID IN PERICARDIAC SAC

To the Editor:—*How often is bleeding found in the pericardiac sac on opening the pericardium for heart operations in rheumatic valvular disease or in coronary artery disease? Where does the bleeding usually come from?*

Aaron N. Gorelik, M.D., Bronx, N. Y.

Answer.—Hemorrhagic fluid is rarely found at operation for rheumatic valvular disease or for coronary artery disease. The pericardiac fluid often appears pink as it is sucked out of the chest, but this is due to hemorrhage from the cut pericardiac vessels. A hemorrhagic effusion is not uncommon during the acute stages of rheumatic disease, and sometimes this fluid compresses the heart and removal is indicated. When the inflammation subsides, the hemorrhagic character of the fluid disappears. Large amounts of lemon-yellow fluid high in protein are sometimes found at the time of operation for mitral stenosis. In some cases, the left auricular appendage is inflamed at operation and any mechanical trauma could cause slight superficial capillary oozing. At the time when operation is done for mitral stenosis, the incidence of hemorrhagic pericardiac fluid is rare and probably indicates acute exacerbation of rheumatic infec-

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

tion. As a rule operation is not done during an acute episode of infection. Hemorrhagic fluid is almost never seen at operation for coronary artery disease. A recent infarct rubbing against parietal pericardium may rupture superficial epicardial vessels. An aneurysm or an infarct may rupture, producing hematopericardium, but this condition is not seen at the time of operation.

CONGENITAL ANOMALIES OF VERTEBRAL BODY

To the Editor:—*On routine x-ray examination of the intestine in a 10-year-old boy an unexpected malformation of the fourth lumbar vertebra was found. The corpus was split into two rounded parts that appeared as thickenings of the right and left arc. The central corporal nucleus had failed to ossify. The superior surface of the fifth vertebra was rounded as a result of abnormal pressure. Neurological examination did not show any abnormality. X-ray pictures after air insufflation showed a slight widening of the dural space but no meningocele. Sometimes, he noted tinglings in the left foot. What are the chances of complications, fracture, paralysis, or spondylolisthesis? Also, please discuss reconstructive operations versus conservative treatment.*

M.D., Netherlands.

Answer.—Congenital anomalies of the vertebral bodies including hemivertebra or bifurcation of a vertebral body with underdevelopment of the two halves of the body, such as shown in the figure, very rarely cause any clinical symptoms requiring

Bifurcation of a vertebral body, with underdevelopment of the two halves.

treatment. Fracture, paralysis, or spondylolisthesis are unlikely to occur. Occasionally, adhesions or attachment of the dura to the inner wall of the spinal canal do occur at the site of a spina bifida or a malformation of a vertebral body, such as that shown in the figure. The spinal cord including the dural sac does not grow in length at the same rate as does the vertebral column itself. If there are adhesions between the dura and the bone, this may result in gradually increased tension upon the cauda equina or the spinal cord itself as growth takes place and the bony components increase in length faster than do the spinal cord and dura. This stretch may cause slowly progressing deformities in the feet, such as the so-called clawfoot, and may also produce changes in sensation. This boy should be observed at yearly intervals, and, if the tingling in the left foot becomes more constant or if any type of progressive deformity is noted, it would be wise to consider laminectomy to look for either fibrous bands or adhesions that could be released.

PINWORMS IN THE APPENDIX

To the Editor:—*Is there any basis for the theory that the appendix may be the seat of chronic Enterobius vermicularis (pinworm) infestation? In cases that fail to respond to various treatments, has the appendix ever been removed solely for the purpose of taking away this source of infestation?*

M.D., Ohio.

Answer.—Reports have appeared on the possible causal relation between appendicitis in children and Enterobius vermicularis infection. (Ashburn, L. L.: Appendiceal Oxyuriasis: Its Incidence and Relationship to Appendicitis, *Am. J. Path.* **17**:841, 1941; Velkoff, C. L.: Correlation of Appendicitis and Oxyuris Vermicularis, *Virginia M. Month.* **77**:75, 1950; and Gordon, H.: Appendiceal Oxyuriasis: Study of Its Incidence in 20,969 Extirpated Appendices, *Ann. Int. Med.* **4**:1521, 1931.) It is estimated that in 5 to 10% of all cases of appendicitis in children, sufficient worms are found in the appendix to establish a definite relation between appendicitis and E. vermicularis infection. On this basis, in some cases, the appendix can be the seat of chronic E. vermicularis infection. The appendix, in some rare instances, has been removed solely for the purpose of taking away this possible source of infection; however, in resistive cases of infection, appendectomy cannot be recommended as a cure. The problem of the egg burden of the environment and reinfection would still remain as a source of infection. Many reports have now been published showing the high cure rate obtained with piperazine (Antepar) citrate to warrant giving this relatively new oxyuricide repeated trials, if necessary, before appendectomy is recommended solely for the cure of E. vermicularis infection. (Bumbalo, T. S.; Gustina, F. J., and Oleksiak, R. E.: Treatment of Pinworm Infection (Enterobiasis): Comparative Study of 3 Oxyuricides, *J. Pediat.* **44**:386, 1954; and Brown, H. W., and Chan, K. F.: Treatment of Enterobius Vermicularis Infections with Piperazine, *Am. J. Trop. Med.* **4**:321, 1955.)

STERILIZATION METHODS FOR SMALL OFFICE

To the Editor.—*1. Which form of sterilization is preferred in a small general office—dry heat (oven) or autoclave with steam under pressure? 2. Which form of sterilization best preserves the cutting edges of knives and scissors, rubber goods, and cotton goods?*

Irving Saffran, M.D., Mattapan, Mass.

Answer.—Steam under pressure, provided by an autoclave, is preferred for the sterilization of most items. It has the following advantages: 1. Lower temperatures are required, and therefore the damage to rubber goods and fabrics is less than that caused by the higher temperatures necessary for hot-air (oven) sterilization. 2. Shorter sterilization cycles are required for autoclave sterilization. Cutting edges of knives and scissors are best preserved by sterilization with hot air. Instructions for required time-temperature cycles for packs, gloves, and instruments, as well as for preparation of items for sterilization are supplied by manufacturers of sterilization equipment.

SILICONES

To the Editor:—*The use of a silicone spray for coating ice-cube trays has been recommended. Is there any danger in the ingestion or in the inhalation of silicones?*

R. R. Grayson, M.D., Perryville, Mo.

Answer.—Thus far, there are no implications of damage from any ordinary exposures to silicones. In fact, successful use is being made of silicones as barrier creams for the skin, and some investigators imply therapeutic benefit. At least one silicone enters food products for human consumption in trace amounts as an antifoaming agent, such as in some fruit juices. Some chemicals employed along with silicones as solvents, such as xylene, introduce their own harmful exposures. Two objectionable features have arisen in connection with silicone usage. The first is that eye irritation with lid edema appears, although without demonstrable organic damage. The other is that an atmosphere containing appreciable levels of silicones is disagreeable or discomforting even if not injurious. The potential number of chemicals within the silicone category is so high that in time

some toxic forms may appear. At present, none is known, or, at least, none is known to be marketed. All that has been published about the action of silicones on humans and animals has been summarized by Browning in "Toxicity of Industrial Organic Solvents," New York, Chemical Publishing Company, Inc., 1953.

POSITIVE RESULTS ON SEROLOGIC TESTS DURING PREGNANCY

To the Editor:—*When a patient shows positive results on the Kline, Kahn, and Venereal Disease Research Laboratory tests for syphilis, how would one determine whether this patient has a biological false-positive test and whether treatment is adequate? For example, what criteria does one use to determine whether a patient, who is in the third trimester of pregnancy, needs further treatment? During two previous pregnancies she has been found to have a positive serology and has had, on two previous occasions, 10 million units of penicillin as treatment.* *M.D., West Virginia.*

Answer.—Determination of the fact of the biological false-positive phenomenon in serologic tests for syphilis demands the performance of one of the serologic techniques that demonstrates the antibody specific for treponemal diseases (T. pallidum antibody). These several techniques are immobilization, agglutination, complement fixation, and immune adherence. The inquirer's attention is directed to an article by Moore and Lutz (Natural History of Systemic Lupus Erythematosus: Approach to Its Study Through Chronic Biologic False Positive Reactors, *J. Chron. Dis.* **1**:297, 1955). This article contains a reasonably complete bibliography of the phenomenon of biologic false positivity. It is highly probable that the pregnant patient described does not require any further treatment in spite of the facts that she is pregnant again and that she may have been infected with syphilis. The inquirer should consult Goodwin and Farber (Necessity for Treatment of Pregnant Syphilitic Women During Every Pregnancy, *Am. J. Syph.* **32**:409, 1948). These authors report on 385 women with varying types of syphilitic infection, who had previously been treated with metal chemotherapy or with penicillin and who had then been observed through 596 subsequent pregnancies in which further antisyphilitic treatment was purposely omitted. There was no evidence of syphilis in any of the 596 infants born of these pregnancies. These data indicate that it is not necessary to administer antisyphilitic treatment to a syphilitic woman during every pregnancy. Goodwin and Farber discuss various minor exceptions and the criteria for the desirability of further treatment.

ACNE

To the Editor:—*My experience as school physician seems to indicate that acne in adolescents is helped most by avoiding peanuts, chocolate, and butter and that, vice versa, adolescents with acne drink milk and ice cream by the quarts. I thought it was accepted theory that the sterols in butterfat plus the sex sterols in adolescence bring on acne. I should like to have this question discussed.*

H. W. Liepmann, M.D., Central Valley, N. Y.

Answer.—At puberty the sex sterols, such as testosterone in the male and probably progesterone in the female, stimulate secretion of the sebaceous gland and thus influence acne. Hamilton (*J. Clin. Endocrinol.* **1**:570, 1941), for instance, has established the relationship of testosterone to acne by demonstrating the absence of seborrhea and acne in prepuberal castrates and eunuchoids. But, other factors such as heredity, general health, proper body metabolism, diet, and hygiene of the skin are also involved in the development of acne. One cannot assert with certainty that the sterols in butterfat induce the onset of acne. Experimental evidence, however, showed that, when normal individuals were fed diets high in fat and carbohydrate, there was increased sebaceous secretion. It is the common experience of many that diets rich in fats and carbohydrates aggravate the acne. Though the question of the role of diet in acne is still somewhat unsettled, the generally accepted treatment regimen prescribes limitation of both fats and carbohydrates in the diet, particularly chocolate, nuts, ice cream, cheese, gravy, and, of course, sea foods because of their iodine content.

EYE, EAR, AND TEETH DEFECTS IN YOUNG GIRL

To the Editor:—*A 7-year-old girl at birth was found to have congenital glaucoma, which has been controlled medically. When 6 years of age, she developed bilateral cataracts, which were removed a few months ago, resulting in fair vision. The child has always had poor teeth. The first tooth erupted when the child was 6 months old, but, by the time she was 15 months old, most of the deciduous teeth were destroyed by caries. Her permanent teeth are now very carious. At the age of 6 she developed moderate deafness. Audiometer testing revealed a loss of high tones due to nerve damage. The child has always had dry skin, very dry hair, and brittle nails. There is no loss of sweating. Blood glucose and calcium levels, complete blood cell count, and urine were all within normal limits. Bone age of hands and wrists was normal last year. The child has no other known anomalies. She is alert and intelligent and does well in school. Her present height is 4 ft. (121.9 cm.) (3rd percentile) and her weight is 45 lb. (20.4 kg.) (15th percentile). The child had measles at the age of 2, and chickenpox at the age of 3; both were of a mild nature. There have been no other illnesses. There is no history of rubella during the mother's pregnancy. Could there be a common etiology to these conditions?*

C. Herbert Crane, M.D., Livingston, N. J.

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—Several conditions might be considered to explain the defects in this child, but it seems apparent that rubella in the mother during pregnancy is not responsible. This conclusion is not based merely on a negative history for that disease, since it has been reported that rubella can occur without an exanthem. The defects that are present and the time that some of them developed are not consistent with the usual abnormalities that are attributable to intrauterine infection from rubella. On the basis of the history, it seems most likely that this is a case of congenital ectodermal dysplasia. The dry skin, dry hair, and defective teeth are characteristic of that condition. Two types have been reported: (1) anhidrotic, where the sweat glands are absent, and (2) cases where sweat glands are present. Eye defects are not always observed but have been mentioned by some authors. James (*Acta. pædiat.* **41**:229, 1952) states that ectodermal dysplasia even in fully developed states does not necessarily follow a fixed pattern. Generally, but not always, there seems to be evidence that the condition is inherited. It occurs more often in males than females. There is no cure.

Answer.—The above-described case fits the description of two syndromes that are characterized by the important features described. "Werner's syndrome (Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 8, Philadelphia, Lea & Febiger, 1954, p. 694), progeria, characterized by shortness of stature, canities, premature baldness, cataracts, hypogonadism, tendency to diabetes, calcification of the blood vessels, osteoporosis and metastatic calcification, is a heredofamilial disorder tending to occur in brothers and sisters." Rothmund's syndrome (Rothmund, A.: Ueber Cataracten in Verbindung mit einer eigen thumlichen Hautgegeneration, von Graefes, *Arch. Ophth.* **14**:159, 1868) is also a recessive hereditary disorder, beginning in early childhood. The shortness of stature and the changes in the muscles are not as marked as they are in Werner's syndrome, and the sexual development usually is normal. Cataract occurs in both syndromes. Osteoporosis is not observed in Rothmund's syndrome, and the skin has brownish pigmentation and telangiectasis associated with it. Rothmund's syndrome may occur singly or in siblings. The onset of cataracts is later than in Werner's syndrome. As a rule, sexual organs are not abnormal. Children are alert, intelligent, and socially at their chronological age level. As the disease is a heredofamilial one, treatment does not materially alter the course of development of the affected children. Results of operations for cataract in reported cases have been fair. Both syndromes may occur in incomplete form. The case described above seems to fit better into the Rothmund syndrome category.

GRANULOMA CAUSING DIFFICULTY IN SWALLOWING

To the Editor:—*One year ago a 25-year-old woman began to have difficulty in swallowing. She was advised to take an antispasmodic medicament and to watch her diet. Six months ago, despite use of the medicament, she began to have more difficulty in swallowing, even with soft foods and liquids. She lost 16 lb. (7.3 kg.), her weight dropping to 114 lb. (51.7 kg.). X-ray (barium swallow) examination revealed a smooth, funnel-shaped constriction of the esophagus at the thoracic inlet, extending from 2 cm. above the suprasternal notch to 2 cm. below. The patient has had no serious illnesses other than the childhood diseases, no operations, and no severe injuries. At present, she feels fairly good and has not lost a day of work as a stenographer. Palpation reveals a smooth, rounded mass, very low on the left side of the neck, which moves a little on swallowing; it appears to be at the inferior pole of the left lateral lobe of the thyroid. Esophagoscopy revealed a firm, periesophageal, hard mass constricting the esophagus to a no. 14 F. bougie, and bronchoscopy revealed a mass compressing the trachea at the same level on the left posterior wall, compressing the lumen of the trachea about 25%. A biopsy was made through a standard collar thyroid incision, at which time a tumor was found in the strap muscles of the neck, firmly fixed in the thoracic inlet and immobile. It could not be adequately approached through the neck. The esophagus and the trachea were thoroughly bound in this mass. The great vessels of the neck on the left side were displaced anterolaterally by the mass. Several biopsies were taken of the thyroid gland itself and of the strap muscles and the mass. The latter could not be moved by this approach without doing a splitting incision of the sternum. At the time of surgery, this mass was found to have invaded many things. Two pathologists who, independently, saw the slides were in agreement as to diagnosis—nonspecific chronic granuloma. The skin test for tuberculosis was positive in first strength. The pathologists said there was not the slightest indication that this was a tuberculous granuloma. After three months of treatment with streptomycin, isoniazid, and cortisone, she did not lose or gain any weight whatsoever. She still has the same difficulty in swallowing and still is on an almost entirely liquid and soft diet. I would appreciate suggestions.*

M.D., Illinois.

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—In this inquiry, there appear to be two fundamental problems. There is the problem of the actual diagnosis of the type of granuloma present. If it is felt that the tissue sampled might not truly define the nature of the lesion, there should be no hesitation in making a small incision through the anterior thorax over the second rib, removing the cartilage and a portion of the second rib on the right side, and, with a relatively small procedure, obtaining an excellent sampling of the upper right paramediastinal tissues. The tissue should be removed not only for pathological study but also for immediate insertion of tissues into susceptible animals, such as the rat, guinea pig, and mouse. Special culture mediums for fungi as well as for acid-fast organisms should be inoculated. The second major problem is in the therapeutic approach. First, it should be mentioned that periesophageal granulomas have frequently been excised, with a satisfactory return of swallowing capacity. Even if all of the mediastinal granuloma could not be removed, the procedure might be considered if there was satisfaction that there was no neoplastic character to the granuloma, such as would occur with Hodgkin's disease. Prior to such excision of periesophageal granulomatous tissues, a two-week period, at least, of adequate specific chemotherapy for possible tuberculosis, including both isoniazid and streptomycin, should be given to protect the patient from possible spread of this disease. If Hodgkin's disease is seriously considered, there should be no hesitation in giving deep x-ray therapy. Inasmuch as some swelling may occur with the x-ray therapy, it is the policy of many clinics to pass a small polyethylene nasogastric tube through the esophagus down into the stomach so that, if major swelling should occur during x-ray therapy, there can be adequate food intake without resorting to gastrostomy. Also, if there is the possibility of Hodgkin's disease, a trial of mechlorethamine hydrochloride therapy intravenously should certainly be considered. There is a definite place for dilation of the esophagus in a condition such as the one mentioned, whether it be malignant or on the basis of a purely inflammatory granuloma. Such dilations could be performed over a guide in the form of a swallowed string without major danger of perforation of the esophageal wall. Once an adequate lumen has been obtained, a satisfactory feeding lumen can be maintained by the insertion of a coiled metal esophageal tube of the type so commonly used by English thoracic surgeons, namely a Souttar tube.

Answer.—This is an interesting and difficult case of mediastinal pathology. Most tumors at this level in patients of this age bracket are neurogenic or thyroid in origin. Occasionally, unsuspected tuberculosis of the vertebrae (Pott's disease) may present itself in the form of a cold abscess and produce the above-described symptoms. The description of the operative findings and the pathologists' report of nonspecific chronic granuloma would exclude, however, the above three possibilities. It seems unlikely that a malignant neoplasm, either carcinomatous or lymphosarcomatous, could be tolerated for a year in a patient of this age without producing serious constitutional deterioration. Years ago, Thorotrast was introduced for carotid arteriography. It was frequently employed by needle puncture without "cut down" to delineate the arterial pattern of the intracranial vessels. When this material was inadvertently injected into the perivascular space, it did not produce immediate reaction but later a very hard ligneous reaction was produced by the radioactive material. It is of particular interest that the late appearance of this progressive lesion was obscured by the failure of many patients to remember the diagnostic procedure. In young patients Thorotrast was given after epileptic seizures or fainting spells. The diagnosis is readily established by x-ray, which shows that the radiopaque material is still present, and by chemical ash study of a representative biopsy. The prognosis when this is present is very formidable, unless radical excision is possible. In the absence of the above possibility, the most likely diagnosis in this case is chronic granuloma, as reported by the pathologists. These peculiar lesions have been reported on many occasions by thoracic surgeons and apparently occur in the midmediastinum, usually above the aortic arch; they are most commonly found on thoracic exploration. In 1950, Samson and others (*J. Thoracic Surg.* **19**:333, 1950) reported four cases of mediastinal "tuberculoma," describing clinical pictures quite similar to the one described above. A granuloma is usually considered to be specific in etiology, but a fair number occur that are of undetermined cause. Benign superior vena caval obstruction is a very common complication when the lesion is located on the right paratracheal region. Surgical intervention with partial removal has frequently been done with questionable benefit. In experience with six cases, the pathologists and bacteriologists have not been able to demonstrate the etiological agent. In all probability, the dysphagia will never become complete and the patient will gradually accommodate herself to the partial compression. It might be advisable to have sections from the biopsy reviewed in several tumor centers. The fear of radiation therapy is probably not justified, if small intermittent doses are initiated and dosage is gradually increased.

PARALYSIS FOLLOWING PENICILLIN INJECTION

To the Editor:—*In Queries and Minor Notes, in* The Journal, *March 10, 1956, page 921, is a question regarding flaccid paralysis of a leg occurring within 24 hours after intramuscular injection of penicillin on that side. This occurrence is almost certain to be due to the penicillin having been injected in close proximity to the sciatic nerve. Chances of full recovery within a period of six weeks to six months are quite good. Pain in the distribution of the sciatic nerve during the phase of recovery may occur. Physical therapy consisting of passive exercises or possible splinting of the ankle should be done in the meantime to prevent deformities.*

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